



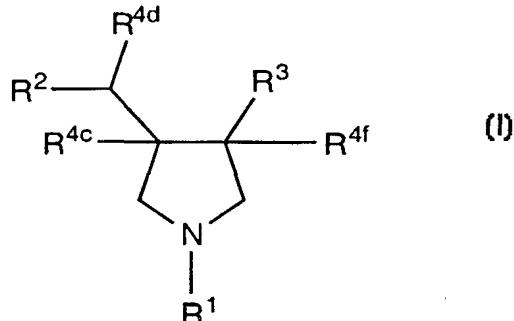
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(54) Title: PYRROLIDINE MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) Abstract

The present invention is directed to pyrrolidine compounds of formula (I): (wherein R¹, R², R³, R^{4c}, R^{4d}, and R^{4f} are defined herein) which are useful as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors CCR-3 and/or CCR-5.



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TITLE OF THE INVENTION

PYRROLIDINE MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

BACKGROUND OF THE INVENTION

5 Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation (reviewed in Schall, Cytokine, 3, 165-183 (1991) and Murphy, Rev. Immun., 12, 593-633 (1994)). There are two classes of chemokines, C-X-C (α) and C-C (β), depending on whether the first two cysteines are separated by a
10 single amino acid (C-X-C) or are adjacent (C-C). The α -chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils, whereas β -chemokines, such as RANTES, MIP-1 α , MIP-1 β , monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin are chemotactic for macrophages, T-cells, eosinophils and basophils (Deng, et al., Nature, 381, 661-666 (1996)).

15 The chemokines bind specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in Horuk, Trends Pharm. Sci., 15, 159-165 (1994)) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal through the associated trimeric G protein, resulting in a rapid increase in intracellular calcium concentration. There are at least seven human chemokine receptors that bind or respond to β -chemokines with the following characteristic pattern: CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1 α , MIP-1 β , MCP-3, RANTES] (Ben-Barruch, et al., J. Biol. Chem., 270, 22123-22128 (1995);
20 Beote, et al., Cell, 72, 415-425 (1993)); CCR-2A and CCR-2B (or "CKR-2A"/"CKR-2A" or "CC-CKR-2A"/"CC-CKR-2A") [MCP-1, MCP-3, MCP-4]; CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin, RANTES, MCP-3] (Combadiere, et al., J. Biol. Chem., 270, 16491-16494 (1995); CCR-4 (or "CKR-4" or "CC-CKR-4") [MIP-1 α , RANTES, MCP-1] (Power, et al., J. Biol. Chem., 270, 19495-19500 (1995)); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1 α , RANTES, MIP-1 β] (Sanson, et al., Biochemistry, 35, 3362-3367 (1996)); and the Duffy blood-group antigen [RANTES, MCP-1] (Chaudhun, et al., J. Biol. Chem., 269, 7835-7838 (1994)). The β -chemokines include eotaxin, MIP ("macrophage inflammatory protein"), MCP ("monocyte chemoattractant protein") and RANTES ("regulation-upon-activation, normal T expressed and secreted").

Chemokine receptors, such as CCR-1, CCR-2, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CXCR-3, CXCR-4, have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases, including asthma, rhinitis and allergic diseases, as well as autoimmune pathologies such as 5 rheumatoid arthritis and atherosclerosis. A review of the role of chemokines in allergic inflammation is provided by Kita, H., et al., J. Exp. Med. 183, 2421-2426 (1996). An antagonist of the CCR3 receptor, Met-chemokine beta 7, has been proposed to be useful in ameliorating leukocyte infiltration associated with allergic 10 inflammation (Nibbs, et al., J. Immunol., 164, 1488-1497 (2000)). Accordingly, agents which modulate chemokine receptors would be useful in such disorders and diseases. Compounds which modulate chemokine receptors would be especially useful in the treatment and prevention of atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and particularly bronchial asthma.

A retrovirus designated human immunodeficiency virus (HIV-1) is the 15 etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV.

Certain compounds have been demonstrated to inhibit the replication 20 of HIV, including soluble CD4 protein and synthetic derivatives (Smith, et al., Science, 238, 1704-1707 (1987)), dextran sulfate, the dyes Direct Yellow 50, Evans Blue, and certain azo dyes (U.S. Patent No. 5,468,469). Some of these antiviral agents have been shown to act by blocking the binding of gp120, the coat protein of HIV, to its target, the CD4 glycoprotein of the cell.

Entry of HIV-1 into a target cell requires cell-surface CD4 and 25 additional host cell cofactors. Fusin has been identified as a cofactor required for infection with virus adapted for growth in transformed T-cells, however, fusin does not promote entry of macrophagotropic viruses which are believed to be the key pathogenic strains of HIV in vivo. It has recently been recognized that for efficient 30 entry into target cells, human immunodeficiency viruses require the chemokine receptors CCR-5 and CXCR-4, as well as the primary receptor CD4 (Levy, N. Engl. J. Med., 335(20), 1528-1530 (Nov. 14 1996). The principal cofactor for entry mediated by the envelope glycoproteins of primary macrophage-trophic strains of HIV-1 is CCR5, a receptor for the β -chemokines RANTES, MIP-1 α and MIP-1 β (Deng, et al., 35 Nature, 381, 661-666 (1996)). HIV attaches to the CD4 molecule on cells through a

region of its envelope protein, gp120. It is believed that the CD-4 binding site on the gp120 of HIV interacts with the CD4 molecule on the cell surface, and undergoes conformational changes which allow it to bind to another cell-surface receptor, such as CCR5 and/or CXCR-4. This brings the viral envelope closer to the cell surface and 5 allows interaction between gp41 on the viral envelope and a fusion domain on the cell surface, fusion with the cell membrane, and entry of the viral core into the cell. It has been shown that β -chemokine ligands prevent HIV-1 from fusing with the cell (Dragic, et al., *Nature*, 381, 667-673 (1996)). It has further been demonstrated that a complex of gp120 and soluble CD4 interacts specifically with CCR-5 and inhibits the 10 binding of the natural CCR-5 ligands MIP-1 α and MIP-1 β (Wu, et al., *Nature*, 384, 179-183 (1996); Trkola, et al., *Nature*, 384, 184-187 (1996)).

Humans who are homozygous for mutant CCR-5 receptors which do not serve as co-receptors for HIV-1 in vitro appear to be unusually resistant to HIV-1 infection and are not immuno-compromised by the presence of this genetic variant 15 (*Nature*, 382, 722-725 (1996)). Absence of CCR-5 appears to confer protection from HIV-1 infection (*Nature*, 382, 668-669 (1996)). Other chemokine receptors may be used by some strains of HIV-1 or may be favored by non-sexual routes of transmission. Although most HIV-1 isolates studied to date utilize CCR-5 or fusin, some can use both as well as the related CCR-2B and CCR-3 as co-receptors (*Nature* 20 *Medicine*, 2(11), 1240-1243 (1996)). Nevertheless, drugs targeting chemokine receptors may not be unduly compromised by the genetic diversity of HIV-1 (Zhang, et al., *Nature*, 383, 768 (1996)). Accordingly, an agent which could block chemokine receptors in humans who possess normal chemokine receptors should prevent infection in healthy individuals and slow or halt viral progression in infected patients. 25 By focusing on the host's cellular immune response to HIV infection, better therapies towards all subtypes of HIV may be provided. These results indicate that inhibition of chemokine receptors presents a viable method for the prevention or treatment of infection by HIV and the prevention or treatment of AIDS.

The peptides eotaxin, RANTES, MIP-1 α , MIP-1 β , MCP-1, and MCP-30 3 are known to bind to chemokine receptors. As noted above, the inhibitors of HIV-1 replication present in supernatants of CD8+ T cells have been characterized as the β -chemokines RANTES, MIP-1 α and MIP-1 β .

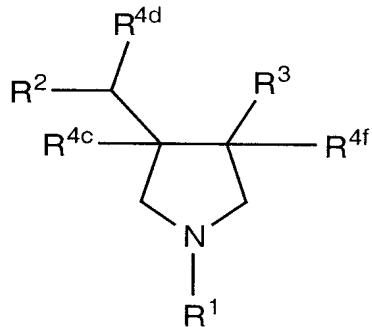
SUMMARY OF THE INVENTION

The present invention is directed to compounds which are modulators of chemokine receptor activity and are useful in the prevention or treatment of certain inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as 5 autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which chemokine receptors are involved.

The present invention is further concerned with compounds which 10 inhibit the entry of human immunodeficiency virus (HIV) into target cells and are of value in the prevention of infection by HIV, the treatment of infection by HIV and the prevention and/or treatment of the resulting acquired immune deficiency syndrome (AIDS). The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for 15 the prevention and treatment of AIDS and viral infection by HIV.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula I:



5

I

wherein:

R¹ is -X-R⁸, wherein X is selected from the group consisting of:

- (1) -CH₂-,
- (2) -CO-,
- (3) -CH₂CH₂-,
- (4) -CH₂CH₂CH₂-, and
- (5) -CH(C₁-6 alkyl)-,

and wherein R⁸ is selected from:

phenyl, naphthyl, biphenyl, fluorenyl, indenyl, indanyl, dihydronaphthyl,
 15 tetrahydronaphthyl, octahydronaphthyl, adamantyl, and heterocycle,
 which may be unsubstituted or substituted, where the substituents are
 independently selected from:

- (a) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl,
 alkenyl, or alkynyl is unsubstituted or substituted, wherein the
 20 substituents are independently selected from:
 - (i) hydroxy,
 - (ii) halogen,
 - (iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently
 selected from hydrogen, C₁-6 alkyl, C₂-6 alkenyl, and
 C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is
 25 unsubstituted or substituted, wherein the substituents
 are independently selected from:

5 (A) phenyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

10 (B) naphthyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

15 (C) heterocycle,unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

20 (D) hydroxy,
(E) -O(C₁-6 alkyl),
(F) -CO₂(C₁-6 alkyl),
(G) -S(O)_n-(C₁-6 alkyl), wherein n is an
integer selected from 0, 1 and 2,

25 (H) halogen,
(I) -NH₂,
(J) -NH(C₁-6 alkyl), and
(K) -N(C₁-6 alkyl)(C₁-6 alkyl),

30 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,

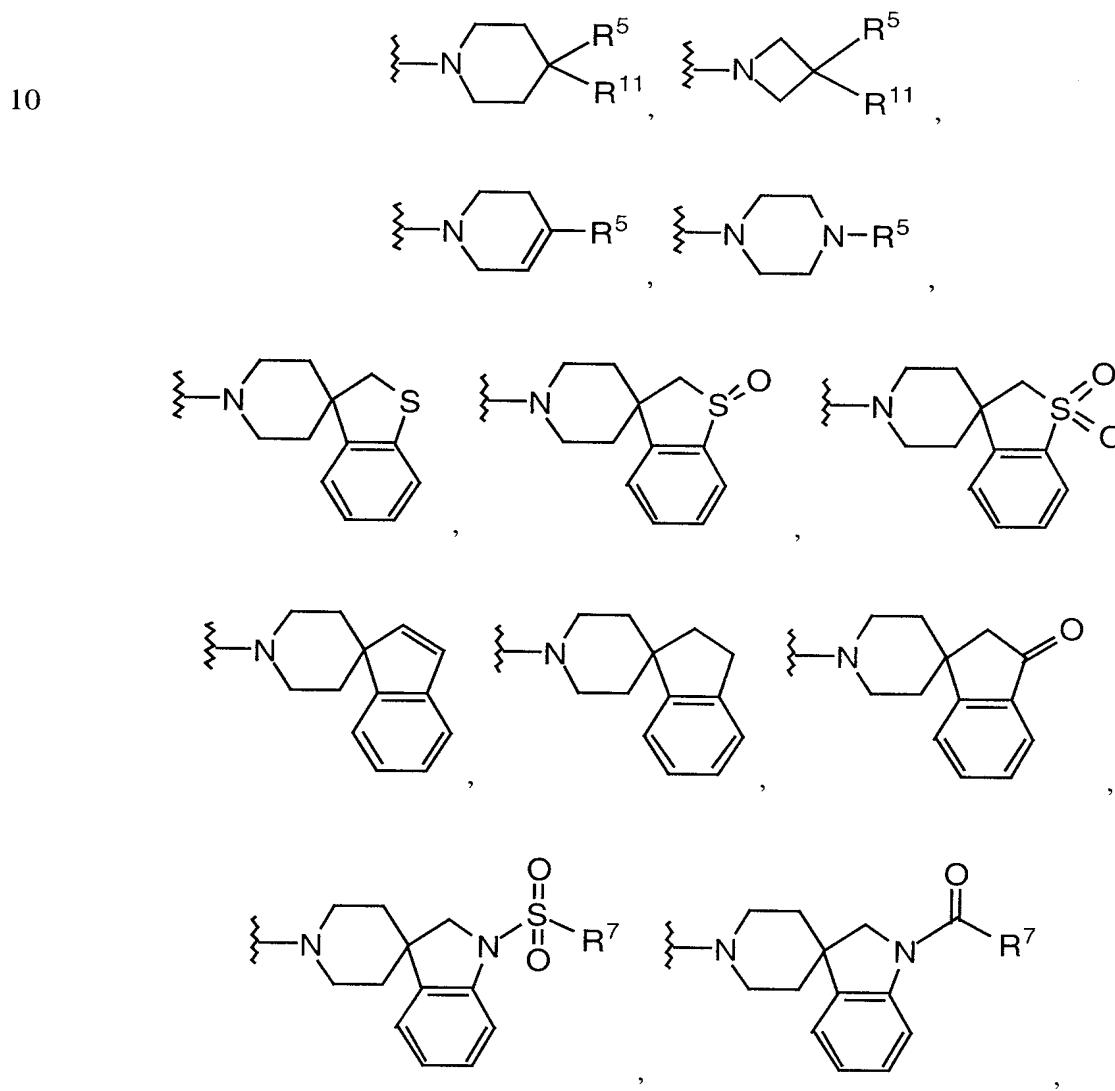
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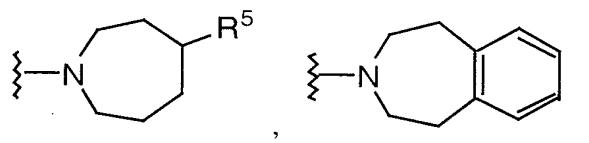
(ix) -S(O)₂-NR⁹R¹⁰, wherein n is an integer selected from 0, 1 and 2,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
5 (xii) -S(O)_n-R⁹,
(xiii) -CF₃,
(xiv) -CHF₂,
(xv) -CH₂F,
(xvi) -O-R⁹,
10 (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
(xviii) phenyl,
(xix) naphthyl,
(xx) indenyl,
(xxi) indanyl,
15 (xxii) heterocycle,
(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,
(xxv) -CO-indenyl,
(xxvi) -CO-indanyl,
20 (xxvii) -CO-heterocycle,
(xxviii) -OCO-R⁹,
(xxix) -OCO₂R⁹, and
(xxx) -CO-R⁹,
(b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the
25 alkyl, alkenyl, or alkynyl is unsubstituted or substituted,
wherein the substituents are independently selected from:
(i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰,
30 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,

- (ix) -S(O)₂-NR⁹R¹⁰,
- (x) -NR⁹S(O)₂-R¹⁰,
- (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
- (xii) -S(O)_n-R⁹,
- 5 (xiii) -CF₃,
- (xiv) -CHF₂,
- (xv) -CH₂F,
- (xvii) -O-R⁹,
- (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
- 10 (xviii) phenyl,
- (xix) naphthyl,
- (xx) indenyl,
- (xxi) indanyl,
- (xxii) heterocycle,
- 15 (xxiii) -CO-phenyl,
- (xxiv) -CO-naphthyl,
- (xxv) -CO-indenyl,
- (xxvi) -CO-indanyl,
- (xxvii) -CO-heterocycle,
- 20 (xxviii) -OCO-R⁹,
- (xxix) -OCO₂-R⁹, and
- (xxx) -CO-R⁹,
- (c) -NO₂,
- (d) hydroxy,
- 25 (e) halogen,
- (f) -NR⁹R¹⁰,
- (g) -NR⁹-COR¹⁰,
- (h) -NR⁹-CO₂R¹⁰,
- (i) -CO-NR⁹R¹⁰,
- 30 (j) -OCO-NR⁹R¹⁰,
- (k) -NR⁹CO-NR⁹R¹⁰,
- (l) -S(O)₂-NR⁹R¹⁰,
- (m) -NR⁹S(O)₂-R¹⁰,
- (n) -NR⁹S(O)₂-NR⁹R¹⁰,

- (o) $-\text{S}(\text{O})_n\text{R}^9$,
- (p) $-\text{CF}_3$,
- (q) $-\text{CHF}_2$,
- (r) $-\text{CH}_2\text{F}$,
- 5 (s) $-\text{OCO-R}^9$,
- (t) $-\text{OCO}_2\text{R}^9$, and
- (u) $-\text{CO-R}^9$;

R^2 is selected from the group consisting of:





wherein R⁵ is a selected from:

- (1) -NR⁶CO-O-R⁷, wherein R⁶ is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkyl-C₅₋₆ cycloalkyl, and R⁷ is C₁₋₆ alkyl, C₅₋₆ cycloalkyl, benzyl or phenyl, wherein the alkyl, cycloalkyl, benzyl or phenyl is unsubstituted or substituted with halogen, C₁₋₃alkyl, C₁₋₃alkoxy or trifluoromethyl,
- (2) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,
- (3) -pyridyl,
- (4) -thienyl,
- (5) -C₁₋₆alkyl-phenyl, -C₁₋₆alkyl-naphthyl, -C₁₋₆alkyl-indenyl, -C₁₋₆alkyl-indanyl, and -C₁₋₆alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl; and wherein the -C₁₋₆alkyl is optionally substituted with oxo, hydroxy, C₁₋₆alkoxy, acetoxy, or halogen,
- (6) -O-C₁₋₆alkyl-phenyl, -O-C₁₋₆alkyl-naphthyl, -O-C₁₋₆alkyl-indenyl, -O-C₁₋₆alkyl-indanyl, and -O-C₁₋₆alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,
- (7) -C₁₋₄alkyl-O-C₁₋₄alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl, and
- (8) -C₁₋₄alkyl-S(O)_n-C₁₋₄alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl,

C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl;

and wherein R¹¹ is a selected from:

5 (1) -hydrogen,
(2) -OH,
(3) -C₁₋₆alkyl, and
(4) -halogen;

R³ is selected from the group consisting of:

10 (1) -CHO,
(2) -CO₂(C₁₋₆ alkyl),
(3) -CO-R⁹,
(4) -CONR⁹R¹⁰,
(5) -CONR⁹-COR¹⁰,
15 (6) -CONR⁹-CO₂R¹⁰,
(7) -C(R⁹)(OR⁹)(OR¹⁰),
(8) -C(R⁹)(SR⁹)(SR¹⁰),
(9) -C(R⁹)(OR¹⁴)(OR¹⁵), wherein R¹⁴ and R¹⁵ are joined together in a
20 C₂₋₃ alkyl group to form a 5- or 6-membered ring which is substituted
with R¹² and R¹³ wherein:

R¹² and R¹³ are independently selected from:

25 (a) hydrogen,
(b) -CO₂(C₁₋₆ alkyl),
(c) hydroxy,
(d) halogen,
(e) -NR⁹R¹⁰,
(f) -NR⁹-COR¹⁰,
(g) -NR⁹-CO₂R¹⁰,
(h) -CF₃,
30 (i) -CHF₂,
(j) -CH₂F,
(k) -O-R⁹,

(l) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

(i) -CO₂(C₁-6 alkyl),
5 (ii) hydroxy,
(iii) halogen,
(iv) -NR⁹R¹⁰,
(v) -NR⁹-COR¹⁰,
(vi) -NR⁹-CO₂R¹⁰,
10 (vii) phenyl,
(viii) -CF₃,
(ix) -CHF₂,
(x) -CH₂F, and
(xi) -O-R⁹,

15 (p) phenyl or heterocycle, wherein the phenyl or heterocycle is unsubstituted or substituted, wherein the substituents are independently selected from:

(i) -CO₂(C₁-6 alkyl),
(ii) hydroxy,
20 (iii) halogen,
(iv) -NR⁹R¹⁰,
(v) -NR⁹-COR¹⁰,
(vi) -NR⁹-CO₂R¹⁰,
(vii) phenyl,
25 (viii) -CF₃,
(ix) -CHF₂,
(x) -CH₂F, and
(xi) -O-R⁹,

(11) -C(R⁹)(SR¹⁴)(SR¹⁵),
30 (12) -cyclopentyl, which is substituted with R¹² and R¹³,
(13) -cyclohexyl, which is substituted with R¹² and R¹³,
(14) -tetrahydrofuranyl, which is substituted with R¹² and R¹³,
(15) -tetrahydropyranyl, which is substituted with R¹² and R¹³;

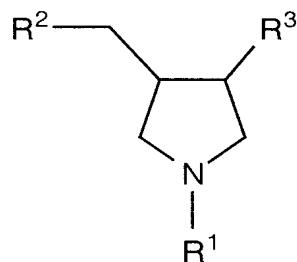
R^{4c} , R^{4d} , and R^{4f} are independently selected from the group consisting of:

- (1) hydrogen, and
- (2) C1-6 alkyl;

5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

Preferred compounds of the present invention include those of formula

Ia:



10

Ia

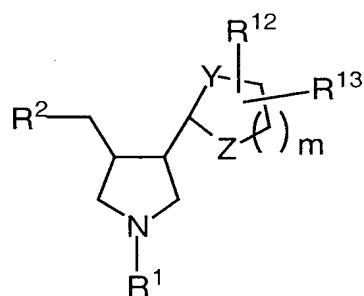
wherein:

R^1 , R^2 and R^3 are defined herein;

and pharmaceutically acceptable salts and individual diastereomers thereof.

15

Preferred compounds of the present invention include those of the formula Ib:



Ib

wherein:

20 R^1 is $-X-R^8$, wherein X is selected from the group consisting of:

- (1) $-CH_2-$,

- (2) -CO-, and
- (3) -CH₂CH₂-,

and wherein R⁸ is a selected from:

5 phenyl, naphthyl, biphenyl, fluorenyl, indenyl, indanyl, dihydronaphthyl,
tetrahydronaphthyl, octahydronaphthyl, adamantyl, and heterocycle,
which may be unsubstituted or substituted, where the substituents are
independently selected from:

10 (a) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl,
alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are
independently selected from:

15 (i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently
selected from hydrogen, C₁-6 alkyl, C₂-6 alkenyl, and
C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is
unsubstituted or substituted, where the substituents are
independently selected from:

20 (A) phenyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

25 (B) naphthyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

30 (C) heterocycle,unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,

35

-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

(D) hydroxy,
5 (E) -O(C₁-6 alkyl),
(F) -CO₂(C₁-6 alkyl),
(G) -S(O)_n(C₁-6 alkyl), wherein n is an
10 integer selected from 0, 1 and 2,
(H) halogen,
(I) -NH₂,
(J) -NH(C₁-6 alkyl), and
(K) -N(C₁-6 alkyl)(C₁-6 alkyl),
(iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
15 (vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,
(ix) -S(O)_n-NR⁹R¹⁰, wherein n is an integer selected from
20 0, 1 and 2,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
(xii) -S(O)_n-R⁹,
(xiii) -CF₃,
25 (xiv) -CHF₂,
(xv) -CH₂F,
(xvi) -O-R⁹,
(xvii) -O(C₁-6 alkyl)-O-R⁹,
(xviii) phenyl,
30 (xix) naphthyl,
(xx) indenyl,
(xxi) indanyl,
(xxii) heterocycle,
(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,

(xxv) -CO-indenyl,
(xxvi) -CO-indanyl,
(xxvii) -CO-heterocycle,
(xxviii) -OCO-R⁹,
5 (xxix) -OCO₂-R⁹, and
(xxx) -CO-R⁹,

(b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

10 (i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰,
(iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
15 (vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,
(ix) -S(O)₂-NR⁹R¹⁰,
(x) -NR⁹S(O)₂-R¹⁰,
20 (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
(xii) -S(O)_n-R⁹,
(xiii) -CF₃,
(xiv) -CHF₂,
(xv) -CH₂F,
25 (xvii) -O-R⁹,
(xviii) -O(C₁₋₆ alkyl)-O-R⁹,
(xix) phenyl,
(xx) naphthyl,
30 (xxi) indenyl,
(xxii) heterocycle,
(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,
(xxv) -CO-indenyl,
35 (xxvi) -CO-indanyl,

- (xxvii) -CO-heterocycle,
- (xxviii) -OCO-R⁹,
- (xxix) -OCO₂-R⁹, and
- (xxx) -CO-R⁹,

5 (c) -NO₂,

(d) hydroxy,

(e) halogen,

(f) -NR⁹R¹⁰,

10 (g) -NR⁹-COR¹⁰,

(h) -NR⁹-CO₂R¹⁰,

(i) -CO-NR⁹R¹⁰,

(j) -OCO-NR⁹R¹⁰,

(k) -NR⁹CO-NR⁹R¹⁰,

(l) -S(O)₂-NR⁹R¹⁰,

15 (m) -NR⁹S(O)₂-R¹⁰,

(n) -NR⁹S(O)₂-NR⁹R¹⁰,

(o) -S(O)_n-R⁹,

(p) -CF₃,

(q) -CHF₂,

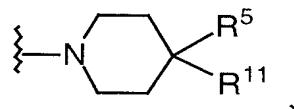
20 (r) -CH₂F,

(s) -OCO-R⁹,

(t) -OCO₂-R⁹, and

(u) -CO-R⁹;

25 R² is:



wherein R⁵ is a selected from:

(1) -NR⁶CO-O-R⁷, wherein R⁶ is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkyl-C₅₋₆ cycloalkyl, and R⁷ is C₁₋₆ alkyl, C₅₋₆ cycloalkyl, benzyl or phenyl, wherein the alkyl, cycloalkyl, benzyl or phenyl is unsubstituted or substituted with halogen, C₁₋₃alkyl, C₁₋₃alkoxy or trifluoromethyl,

30

(2) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,

5 (3) -pyridyl,

(4) -thienyl,

(5) -C₁-6alkyl-phenyl, -C₁-6alkyl-naphthyl, -C₁-6alkyl-indenyl, -C₁-6alkyl-indanyl, and -C₁-6alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl;

10 and wherein the -C₁-6alkyl is optionally substituted with oxo, hydroxy, C₁-6alkoxy, acetoxy, or halogen,

(6) -O-C₁-6alkyl-phenyl, -O-C₁-6alkyl-naphthyl,

15 -O-C₁-6alkyl-indenyl, -O-C₁-6alkyl-indanyl, and -O-C₁-6alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,

20 (7) -C₁-4alkyl-O-C₁-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl, and

(8) -C₁-4alkyl-S(O)_n-C₁-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl;

25 and wherein R¹¹ is selected from:

(1) -hydrogen,

(2) -OH,

30 (3) -C₁-6alkyl, and

(4) -halogen;

R¹² and R¹³ are independently selected from:

35 (1) hydrogen,

(2) -CO₂(C₁-6 alkyl),

(3) hydroxy,
(4) halogen,
(5) -NR⁹R¹⁰,
(6) -NR⁹-COR¹⁰,
5 (7) -NR⁹-CO₂R¹⁰,
(8) -CF₃,
(9) -CHF₂,
(10) -CH₂F,
10 (11) -O-R⁹,
(12) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:
(a) -CO₂(C₁-6 alkyl),
15 (b) hydroxy,
(c) halogen,
(d) -NR⁹R¹⁰,
(e) -NR⁹-COR¹⁰,
(f) -NR⁹-CO₂R¹⁰,
20 (g) phenyl,
(h) -CF₃,
(i) -CHF₂,
(j) -CH₂F, and
(k) -O-R⁹,
25 (14) phenyl or heterocycle, wherein the phenyl or heterocycle is unsubstituted or substituted, wherein the substituents are independently selected from:
(a) -CO₂(C₁-6 alkyl),
(b) hydroxy,
(c) halogen,
30 (d) -NR⁹R¹⁰,
(e) -NR⁹-COR¹⁰,
(f) -NR⁹-CO₂R¹⁰,
(g) phenyl,
(h) -CF₃,
35 (i) -CHF₂,

- (j) -CH₂F, and
- (k) -O-R⁹,

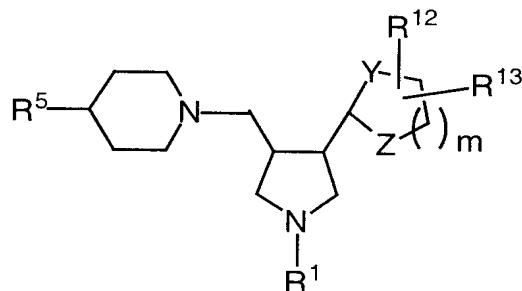
Y and Z are independently selected from: C₁ alkyl, -O-, -S(O)_n- and
5 -N(R⁹)-;

m is an integer selected from 1 and 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10

More preferred compounds of the present invention include those of the formula Ic:

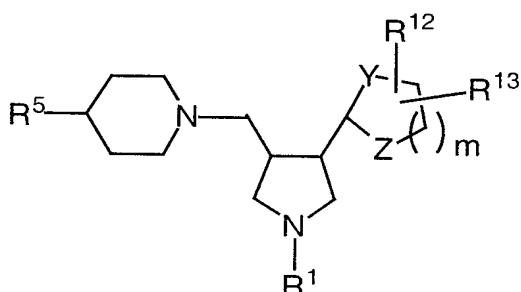


15 wherein:

R¹, R⁵, R¹², R¹³, Y, Z and m are defined herein;

and pharmaceutically acceptable salts and individual diastereomers thereof.

20 Highly preferred compounds of the present invention further include those of the formula Id:



Id

wherein:

R¹ is -X-R⁸, wherein X is selected from the group consisting of:

(1) -CH₂-, and

5 (2) -CO-,

and wherein R⁸ is selected from:

phenyl, naphthyl, indenyl, indanyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, dihydrobenzofuranyl, methylenedioxybenzoyl, benzopyrazolyl, and benzotriazolyl, which may be unsubstituted or substituted, where the substituents are independently selected from:

10 (a) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:

(i) hydroxy,

15 (ii) halogen,

(iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁-6 alkyl, C₂-6 alkenyl, and C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:

20 (A) phenyl, unsubstituted or substituted, where the substituents are independently selected from: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl), -N(C₁-6 alkyl)(C₁-6 alkyl), or trifluoromethyl,

25 (B) naphthyl, unsubstituted or substituted, where the substituents are independently selected from: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl), -N(C₁-6 alkyl)(C₁-6 alkyl), or trifluoromethyl,

30 (C) heterocycle,unsubstituted or substituted,

35

wherein the substituents are independently selected from: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)(C₁₋₆ alkyl), or trifluoromethyl,

5 (D) hydroxy,
(E) -O(C₁₋₆ alkyl),
(F) -CO₂(C₁₋₆ alkyl),
10 (G) -S(O)_n-(C₁₋₆ alkyl), wherein n is an integer selected from 0, 1 and 2,
(H) halogen,
(I) -NH₂,
(J) -NH(C₁₋₆ alkyl), and
15 (K) -N(C₁₋₆ alkyl)(C₁₋₆ alkyl),
(iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
20 (viii) -NR⁹CO-NR⁹R¹⁰,
(ix) -S(O)_n-NR⁹R¹⁰, wherein n is an integer selected from 0, 1 and 2,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
25 (xii) -S(O)_n-R⁹,
(xiii) -CF₃,
(xiv) -CHF₂,
(xv) -CH₂F,
(xvi) -O-R⁹,
30 (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
(xviii) phenyl,
(xix) naphthyl,
(xx) indenyl,
(xxi) indanyl,
35 (xxii) heterocycle,

(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,
(xxv) -CO-indenyl,
(xxvi) -CO-indanyl,
5 (xxvii) -CO-heterocycle,
(xxviii) -OCO-R⁹,
(xxix) -OCO₂-R⁹, and
(xxx) -CO-R⁹,

10 (b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

(i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰,
15 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,
20 (ix) -S(O)₂-NR⁹R¹⁰,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
(xii) -S(O)_n-R⁹,
(xiii) -CF₃,
25 (xiv) -CHF₂,
(xv) -CH₂F,
(xvii) -O-R⁹,
(xviii) -O(C₁₋₆ alkyl)-O-R⁹,
(xix) phenyl,
30 (xx) naphthyl,
(xxi) indenyl,
(xxii) indanyl,
(xxiii) heterocycle,
(xxiv) -CO-phenyl,
35 (xxiv) -CO-naphthyl,

- (xxv) -CO-indenyl,
- (xxvi) -CO-indanyl,
- (xxvii) -CO-heterocycle,
- (xxviii) -OCO-R⁹,
- 5 (xxix) -OCO₂-R⁹, and
- (xxx) -CO-R⁹,
- (c) -NO₂,
- (d) hydroxy,
- (e) halogen,
- 10 (f) -NR⁹R¹⁰,
- (g) -NR⁹-COR¹⁰,
- (h) -NR⁹-CO₂R¹⁰,
- (i) -CO-NR⁹R¹⁰,
- (j) -OCO-NR⁹R¹⁰,
- 15 (k) -NR⁹CO-NR⁹R¹⁰,
- (l) -S(O)₂-NR⁹R¹⁰,
- (m) -NR⁹S(O)₂-R¹⁰,
- (n) -NR⁹S(O)₂-NR⁹R¹⁰,
- (o) -S(O)_n-R⁹,
- 20 (p) -CF₃,
- (q) -CHF₂,
- (r) -CH₂F,
- (s) -OCO-R⁹,
- (t) -OCO₂-R⁹, and
- 25 (u) -CO-R⁹;

wherein R⁵ is a selected from:

- (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,
- 30 (2) -C₁₋₆alkyl-phenyl, -C₁₋₆alkyl-naphthyl, -C₁₋₆alkyl-indenyl, -C₁₋₆alkyl-indanyl, and -C₁₋₆alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁₋₆alkyl,

C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl;
 and wherein the -C₁-6alkyl is optionally substituted with oxo, hydroxy, C₁-6alkoxy, acetoxy, or halogen,

5 (3) -O-C₁-6alkyl-phenyl, -O-C₁-6alkyl-naphthyl,
 -O-C₁-6alkyl-indenyl, -O-C₁-6alkyl-indanyl, and
 -O-C₁-6alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,

10 (4) -C₁-4alkyl-O-C₁-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl, and

(5) -C₁-4alkyl-S(O)_n-C₁-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl;

15

R¹² and R¹³ are independently selected from:

20 (1) hydrogen,
 (2) -CO₂(C₁-6 alkyl),
 (3) hydroxy,
 (4) halogen,
 (5) -NR⁹R¹⁰,

25 (6) -NR⁹-COR¹⁰,
 (7) -NR⁹-CO₂R¹⁰,
 (8) -CF₃,
 (9) -CHF₂,
 (10) -CH₂F,

30 (11) -O-R⁹,
 (12) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:
 (a) -CO₂(C₁-6 alkyl),

(b) hydroxy,
(c) halogen,
(d) -NR⁹R¹⁰,
(e) -NR⁹-COR¹⁰,
5 (f) -NR⁹-CO₂R¹⁰,
(g) phenyl,
(h) -CF₃,
(i) -CHF₂,
(j) -CH₂F, and
10 (k) -O-R⁹,

(14) phenyl or heterocycle, wherein the phenyl or heterocycle is unsubstituted or substituted, wherein the substituents are independently selected from:

(a) -CO₂(C₁-6 alkyl),
15 (b) hydroxy,
(c) halogen,
(d) -NR⁹R¹⁰,
(e) -NR⁹-COR¹⁰,
(f) -NR⁹-CO₂R¹⁰,
20 (g) phenyl,
(h) -CF₃,
(i) -CHF₂,
(j) -CH₂F, and
(k) -O-R⁹,

25 Y and Z are independently selected from: C₁ alkyl, -O-, -S(O)_n- and -N(R⁹)-;

30 m is an integer selected from 1 and 2;
and pharmaceutically acceptable salts and individual diastereomers thereof.

In the present invention it is preferred that
R¹ is -X-R⁸, wherein X is selected from the group consisting of:
35 (1) -CH₂-, and

(2) -CO-,

and wherein R⁸ is selected from:

phenyl, naphthyl, biphenyl, indenyl, indanyl, and heterocycle,

which may be unsubstituted or substituted, where the substituents are independently selected from:

(a) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:

(i) hydroxy,

(ii) halogen,

(iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁-6 alkyl, C₂-6 alkenyl, and C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:

(A) phenyl, unsubstituted or substituted,

wherein the substituents are

independently selected from: halogen,

hydroxy, C₁-6alkyl, C₁-6alkoxy,

-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),

-N(C₁-6 alkyl)(C₁-6 alkyl), or

trifluoromethyl,

(B) naphthyl, unsubstituted or substituted,

wherein the substituents are

independently selected from: halogen,

hydroxy, C₁-6alkyl, C₁-6alkoxy,

-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),

-N(C₁-6 alkyl)(C₁-6 alkyl), or

trifluoromethyl,

(C) heterocycle,unsubstituted or substituted,

wherein the substituents are

independently selected from: halogen,

hydroxy, C₁-6alkyl, C₁-6alkoxy,

-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),

-N(C₁-6 alkyl)(C₁-6 alkyl), or

trifluoromethyl,
(D) hydroxy,
(E) -O(C₁₋₆ alkyl),
(F) -CO₂(C₁₋₆ alkyl),
5 (G) -S(O)_n-(C₁₋₆ alkyl), wherein n is an integer selected from 0, 1 and 2,
(H) halogen,
(I) -NH₂,
(J) -NH(C₁₋₆ alkyl), and
10 (K) -N(C₁₋₆ alkyl)(C₁₋₆ alkyl),
(iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
15 (viii) -NR⁹CO-NR⁹R¹⁰,
(ix) -S(O)_n-NR⁹R¹⁰, wherein n is an integer selected from 0, 1 and 2,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
20 (xii) -S(O)_n-R⁹,
(xiii) -CF₃,
(xiv) -CHF₂,
(xv) -CH₂F,
(xvi) -O-R⁹,
25 (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
(xviii) phenyl,
(xix) naphthyl,
(xx) indenyl,
(xxi) indanyl,
30 (xxii) heterocycle,
(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,
(xxv) -CO-indenyl,
(xxvi) -CO-indanyl,
35 (xxvii) -CO-heterocycle,

(xxviii) -OCO-R⁹,
(xxix) -OCO₂-R⁹, and
(xxx) -CO-R⁹,

(b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

5 (i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰,
10 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
15 (viii) -NR⁹CO-NR⁹R¹⁰,
(ix) -S(O)₂-NR⁹R¹⁰,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
20 (xii) -S(O)_n-R⁹,
(xiii) -CF₃,
(xiv) -CHF₂,
(xv) -CH₂F,
25 (xvii) -O-R⁹,
(xvii) -O(C₁₋₆ alkyl)-O-R⁹,
(xviii) phenyl,
(xix) naphthyl,
(xx) indenyl,
(xxi) indanyl,
30 (xxii) heterocycle,
(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,
(xxv) -CO-indenyl,
(xxvi) -CO-indanyl,
(xxvii) -CO-heterocycle,
(xxviii) -OCO-R⁹,

- (xxix) $-\text{OCO}_2\text{R}^9$, and
- (xxx) $-\text{CO-R}^9$,
- (c) $-\text{NO}_2$,
- (d) hydroxy,
- 5 (e) halogen,
- (f) $-\text{NR}^9\text{R}^{10}$,
- (g) $-\text{NR}^9\text{-COR}^{10}$,
- (h) $-\text{NR}^9\text{-CO}_2\text{R}^{10}$,
- (i) $-\text{CO-NR}^9\text{R}^{10}$,
- 10 (j) $-\text{OCO-NR}^9\text{R}^{10}$,
- (k) $-\text{NR}^9\text{CO-NR}^9\text{R}^{10}$,
- (l) $-\text{S(O)}_2\text{-NR}^9\text{R}^{10}$,
- (m) $-\text{NR}^9\text{S(O)}_2\text{-R}^{10}$,
- (n) $-\text{NR}^9\text{S(O)}_2\text{-NR}^9\text{R}^{10}$,
- 15 (o) $-\text{S(O)}_n\text{-R}^9$,
- (p) $-\text{CF}_3$,
- (q) $-\text{CHF}_2$,
- (r) $-\text{CH}_2\text{F}$,
- (s) $-\text{OCO-R}^9$,
- 20 (t) $-\text{OCO}_2\text{R}^9$, and
- (u) $-\text{CO-R}^9$.

In the present invention it is even more preferred that

R^1 is $-\text{X-R}^8$, wherein X is selected from the group consisting of:

- 25 (1) $-\text{CH}_2-$, and
- (2) $-\text{CO-}$,

and wherein R^8 is selected from:

phenyl, naphthyl, indenyl, indanyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, dihydrobenzofuranyl, methylenedioxybenzoyl, benzopyrazolyl, 30 and benzotriazolyl, which may be unsubstituted or substituted, where the substituents are independently selected from:

- (a) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:

5 (i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

10 (A) phenyl, unsubstituted or substituted, wherein the substituents are independently selected from: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)(C₁₋₆ alkyl), or trifluoromethyl,

15 (B) naphthyl, unsubstituted or substituted, wherein the substituents are independently selected from: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)(C₁₋₆ alkyl), or trifluoromethyl,

20 (C) heterocycle,unsubstituted or substituted, wherein the substituents are independently selected from: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)(C₁₋₆ alkyl), or trifluoromethyl,

25 (D) hydroxy,
(E) -O(C₁₋₆ alkyl),
(F) -CO₂(C₁₋₆ alkyl),
(G) -S(O)_n-(C₁₋₆ alkyl), wherein n is an integer selected from 0, 1 and 2,

30 (H) halogen,
(I) -NH₂,

35

(J) -NH(C₁₋₆ alkyl), and
(K) -N(C₁₋₆ alkyl)(C₁₋₆ alkyl),

(v) -NR⁹-COR¹⁰,
(vi) -NR⁹-CO₂R¹⁰,
5 (vii) -CO-NR⁹R¹⁰,
(viii) -OCO-NR⁹R¹⁰,
(ix) -NR⁹CO-NR⁹R¹⁰,
(x) -S(O)₂-NR⁹R¹⁰, wherein n is an integer selected from
0, 1 and 2,
10 (xi) -NR⁹S(O)₂-R¹⁰,
(xii) -NR⁹S(O)₂-NR⁹R¹⁰,
(xiii) -S(O)_n-R⁹,
(xiv) -CF₃,
(xv) -CHF₂,
15 (xvi) -CH₂F,
(xvii) -O-R⁹,
(xviii) -O(C₁₋₆ alkyl)-O-R⁹,
(xix) phenyl,
(xx) naphthyl,
20 (xxi) indenyl,
(xxii) indanyl,
(xxiii) heterocycle,
(xxiv) -CO-phenyl,
(xxv) -CO-naphthyl,
25 (xxvi) -CO-indenyl,
(xxvii) -CO-indanyl,
(xxviii) -CO-heterocycle,
(xxix) -OCO-R⁹,
(xxx) -OCO₂-R⁹, and
30 (xxxi) -CO-R⁹,
(b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:
(i) hydroxy,

- (ii) halogen,
- (iii) -NR⁹R¹⁰,
- (iv) -NR⁹-COR¹⁰,
- (v) -NR⁹-CO₂R¹⁰,
- 5 (vi) -CO-NR⁹R¹⁰,
- (vii) -OCO-NR⁹R¹⁰,
- (viii) -NR⁹CO-NR⁹R¹⁰,
- (ix) -S(O)₂-NR⁹R¹⁰,
- (x) -NR⁹S(O)₂-R¹⁰,
- 10 (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
- (xii) -S(O)_n-R⁹,
- (xiii) -CF₃,
- (xiv) -CHF₂,
- (xv) -CH₂F,
- 15 (xvii) -O-R⁹,
- (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
- (xviii) phenyl,
- (xix) naphthyl,
- (xx) indenyl,
- 20 (xxi) indanyl,
- (xxii) heterocycle,
- (xxiii) -CO-phenyl,
- (xxiv) -CO-naphthyl,
- (xxv) -CO-indenyl,
- 25 (xxvi) -CO-indanyl,
- (xxvii) -CO-heterocycle,
- (xxviii) -OCO-R⁹,
- (xxix) -OCO₂-R⁹, and
- (xxx) -CO-R⁹,
- 30 (c) -NO₂,
- (d) hydroxy,
- (e) halogen,
- (f) -NR⁹R¹⁰,
- (g) -NR⁹-COR¹⁰,
- 35 (h) -NR⁹-CO₂R¹⁰,

- (i) -CO-NR⁹R¹⁰,
- (j) -OCO-NR⁹R¹⁰,
- (k) -NR⁹CO-NR⁹R¹⁰,
- (l) -S(O)₂-NR⁹R¹⁰,
- 5 (m) -NR⁹S(O)₂-R¹⁰,
- (n) -NR⁹S(O)₂-NR⁹R¹⁰,
- (o) -S(O)_n-R⁹,
- (p) -CF₃,
- (q) -CHF₂,
- 10 (r) -CH₂F,
- (s) -OCO-R⁹,
- (t) -OCO₂-R⁹, and
- (u) -CO-R⁹.

15 In the present invention it is highly preferred that

R¹ is selected from the group consisting of:

- (1) -CH₂-phenyl,
- (2) -CO-phenyl,
- (3) -CH₂-(2,4-dichlorophenyl),
- 20 (4) -CO-(2,4-dichlorophenyl),
- (5) -CH₂-(2-naphthyl),
- (6) -CO-(1-naphthyl),
- (7) -CH₂-indolyl, and
- (8) -CO-indolyl.

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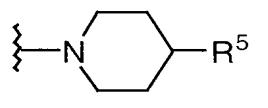
In the present invention it is most preferred that

R¹ is selected from the group consisting of:

- (1) -CH₂-phenyl,
- (2) -CO-phenyl,
- 30 (3) -CH₂-(2,4-dichlorophenyl),
- (4) -CH₂-(7-indolyl), and
- (5) -CO-(7-indolyl).

In the present invention it is preferred that

R² is:

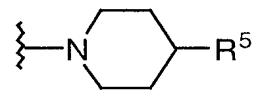


wherein R⁵ is selected from:

- (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- 5 (2) -C₁-6alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl; and wherein the -C₁-6alkyl is optionally substituted with oxo, hydroxy, C₁-6alkoxy, acetoxy, or halogen,
- 10 (3) -O-C₁-6alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- (4) -C₁-4alkyl-O-C₁-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy,
- 15 (5) C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl, and
- (6) -C₁-4alkyl-S(O)_n-C₁-4alkyl-phenyl, wherein n is an integer selected from 0, 1 and 2, and wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl.

20 In the present invention it is more preferred that

R² is:



wherein R⁵ is selected from:

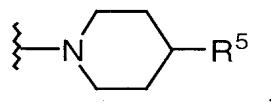
- (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- 25 (2) -C₂-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro, trifluoromethyl, methyl or ethyl and wherein the -C₂-4alkyl is optionally substituted with oxo, hydroxy, halogen, or methoxy,

(3) -C₁-3alkyl-O-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro, trifluoromethyl, methyl or ethyl, and
 (4) -C₁-3alkyl-S(O)_n-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro, trifluoromethyl, methyl or ethyl.

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In the present invention it is still more preferred that

R² is:



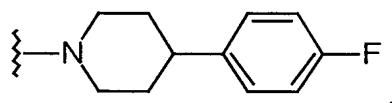
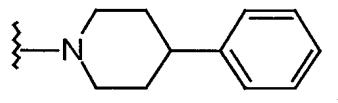
10 wherein R⁵ is selected from:

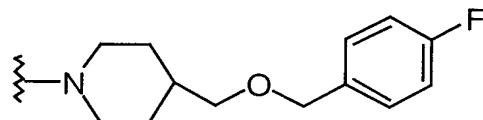
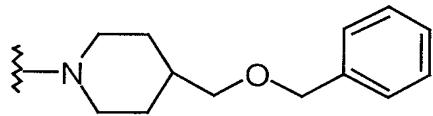
(1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
 (2) -C₃-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro or methyl, and wherein the
 15 -C₃-4alkyl is optionally substituted with oxo, hydroxy, or methoxy,
 (3) -C₁-3alkyl-O-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro or methyl, and
 (4) -C₁-3alkyl-S(O)_n-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro or methyl.

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In the present invention it is highly preferred that

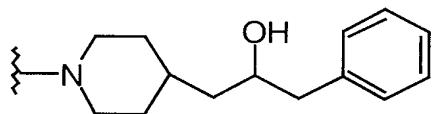
R² is:





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or



In the present invention it is preferred that R³ is selected from the group consisting of:

- (1) -CHO,
- 10 (2) -CO-R¹⁶, wherein R¹⁶ is C₁₋₆ alkyl, wherein the alkyl is unsubstituted or substituted, wherein the substituents are independently selected from:
 - (a) -CO₂(C₁₋₆ alkyl),
 - (b) hydroxy,
 - (c) -O-C₁₋₆ alkyl,
 - (d) halogen, and
 - (e) phenyl,
- 15 (3) -CO₂-R¹⁶,
- (4) -CONH₂,
- 20 (5) -CONR¹⁶R¹⁷, wherein R¹⁷ is hydrogen or is independently selected from the definitions of R¹⁶;
- (6) -CONH-COR¹⁶,
- (7) -C(R¹⁷)(OR¹⁶)(OR¹⁶),
- (8) -C(R¹⁷)(SR¹⁶)(SR¹⁶),

(9) $-\text{C}(\text{R}17)(\text{OR}14)(\text{OR}15)$, wherein $\text{R}14$ and $\text{R}15$ are joined together in a C_{2-3} alkyl group to form a 5- or 6-membered ring which is substituted with $\text{R}12$ and $\text{R}13$ wherein:

$\text{R}12$ and $\text{R}13$ are independently selected from:

5 (a) hydrogen,
 (b) $-\text{CO}_2\text{R}16$,
 (c) hydroxy,
 (d) halogen,
 (e) $-\text{CF}_3$,
 10 (f) $-\text{CHF}_2$,
 (g) $-\text{CH}_2\text{F}$,
 (h) C_{1-6} alkyl, wherein the alkyl is unsubstituted or substituted, wherein the substituents are independently selected from:

15 (i) $-\text{CO}_2(\text{C}_{1-6}$ alkyl),
 (ii) hydroxy,
 (iii) $-\text{O-}\text{C}_{1-6}$ alkyl,
 (iv) halogen, and
 (v) phenyl,
 (i) phenyl, unsubstituted or substituted, wherein the substituents are independently selected from:

20 (i) C_{1-6} alkyl,
 (ii) $-\text{CO}_2(\text{C}_{1-6}$ alkyl),
 (iii) hydroxy,
 (iv) $-\text{O-}\text{C}_{1-6}$ alkyl, and
 (v) halogen,
 25 (10) $-\text{C}(\text{R}17)(\text{SR}14)(\text{SR}15)$,
 (11) cyclopentyl, which is substituted with $\text{R}12$ and $\text{R}13$,
 (12) cyclohexyl, which is substituted with $\text{R}12$ and $\text{R}13$,
 (13) tetrahydrofuryl, which is substituted with $\text{R}12$ and $\text{R}13$,
 30 (14) tetrahydropyranyl, which is substituted with $\text{R}12$ and $\text{R}13$.

In the present invention it is more preferred that $\text{R}3$ is selected from:

(1) $-\text{CH}(\text{OR}14)(\text{OR}15)$, wherein $\text{R}14$ and $\text{R}15$ are joined together in a

C₂-3 alkyl group to form a 5- or 6-membered ring which is substituted with R₁₂ and R₁₃ wherein:

R₁₂ and R₁₃ are independently selected from:

- (a) hydrogen,
- 5 (b) C₁-6 alkyl, wherein the alkyl is unsubstituted or substituted, wherein the substituents are independently selected from:
 - (i) -O-C₁-6 alkyl,
 - (ii) halogen, and
 - (iii) phenyl,
- 10 (c) phenyl, unsubstituted or substituted, wherein the substituents are independently selected from:
 - (i) C₁-6 alkyl,
 - (ii) -O-C₁-6 alkyl,
 - (iii) halogen, and
- 15 (2) -CH(SR₁₄)(SR₁₅),
- (3) -tetrahydrofuryl, which is substituted with R₁₂ and R₁₃,
- (4) -tetrahydropyranyl, which is substituted with R₁₂ and R₁₃.

In the present invention it is preferred that

20 R^{4c}, R^{4d}, and R^{4h} are independently selected from the group consisting of:

- (1) hydrogen, and
- (2) C₁-6 alkyl.

In the present invention it is more preferred that

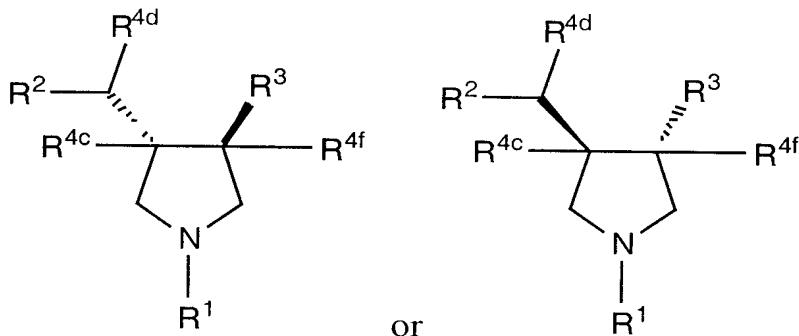
25 R^{4c}, and R^{4h} are each hydrogen and that R^{4d} is selected from the group consisting of hydrogen, and -CH₃.

In the present invention it is most preferred that R^{4c}, R^{4d}, and R^{4h} are each hydrogen.

30 The compounds of the instant invention have at least two asymmetric centers at the ring junction of the substituents bearing R² and R³. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently

produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The relative configurations of the most preferred compounds of this invention are of the trans orientation, i.e. as depicted:

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The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

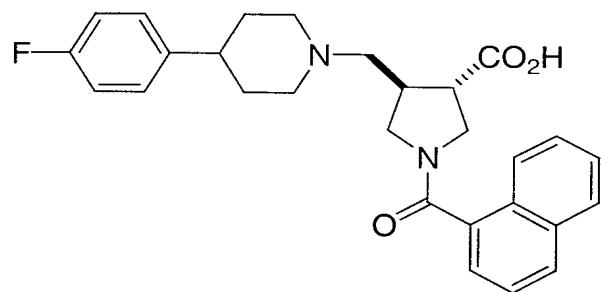
As appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo. Similarly, C₁-8, as in C₁-8alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbons in a linear or branched arrangement, such that C₁-8alkyl specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. The term "heterocycle" as used herein is intended to include the following groups: benzimidazolyl, benzofuranyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, 15 isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, 20 isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, 25 dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl,

dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl,

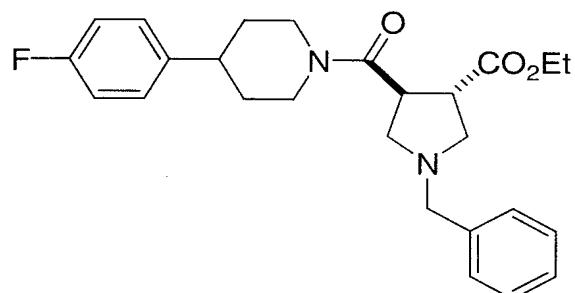
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Exemplifying the invention is the use of the compounds disclosed in the Examples and herein.

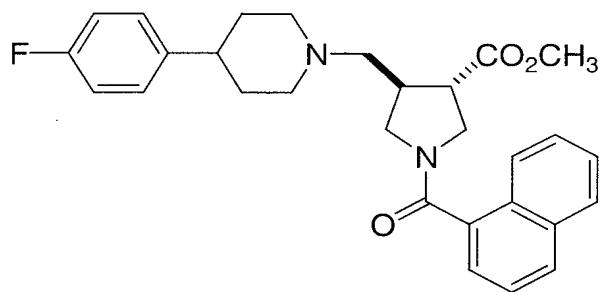
10 Specific compounds within the present invention include a compounds which selected from the group consisting of:



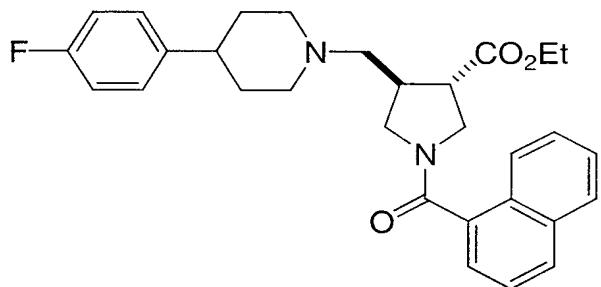
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-carboxypyrrolidine;



15 1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(RS)-(ethoxy carbonyl)pyrrolidine;



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-methoxycarbonylpyrrolidine;



5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-ethoxycarbonylpyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-isopropoxycarbonylpyrrolidine;

10 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-benzyloxycarbonylpyrrolidine;

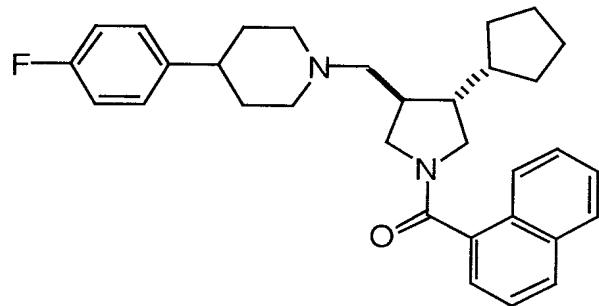
15 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N-ethylaminocarbonyl)pyrrolidine;

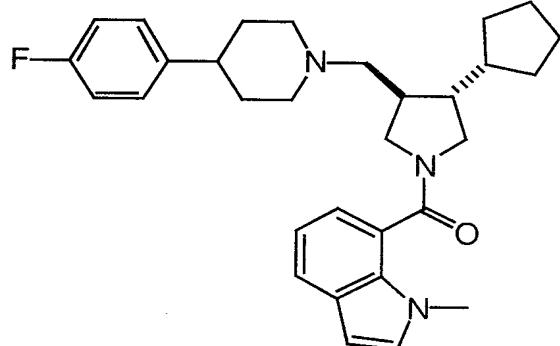
20 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N, N-diethylaminocarbonyl)pyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-acetylpyrrolidine;

5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-benzoylpyrrolidine;

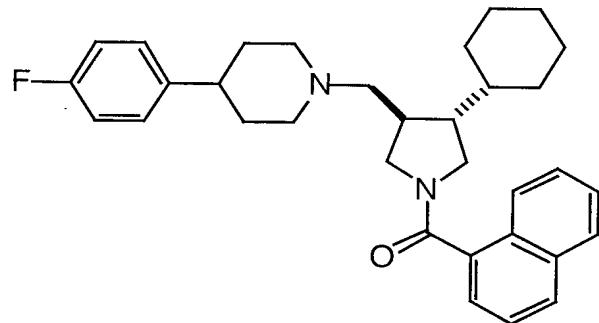


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(cyclopentyl)pyrrolidine;

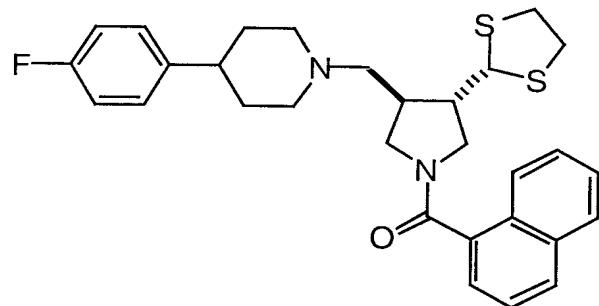


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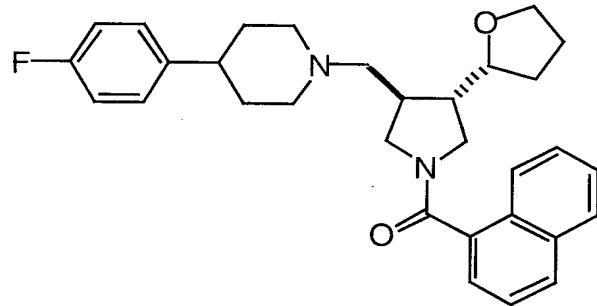
1-(1-Methyl-7-indolecarbonoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinyl methyl)-4-(SR)-(cyclopentyl)pyrrolidine;



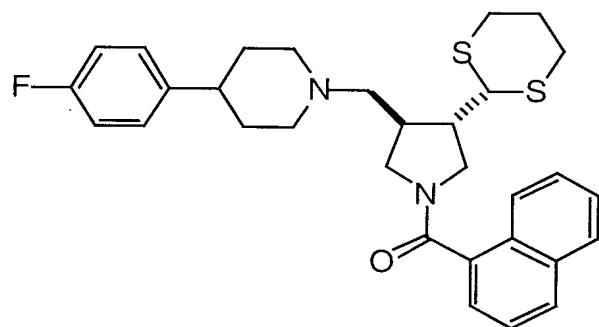
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(cyclohexyl)pyrrolidine;



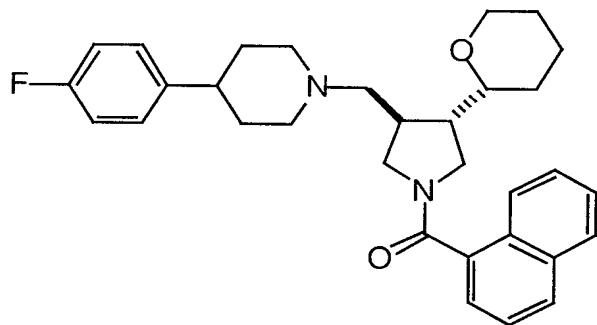
5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dithiolan-2-yl)pyrrolidine;



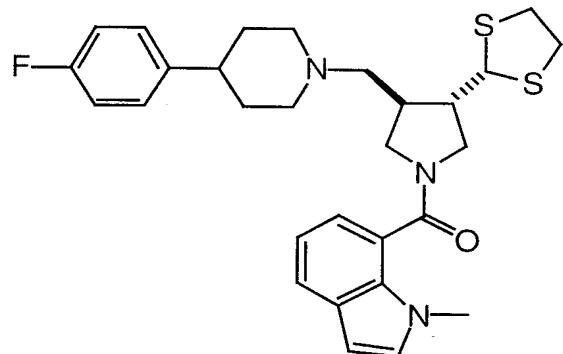
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-tetrahydrofuranyl)pyrrolidine;



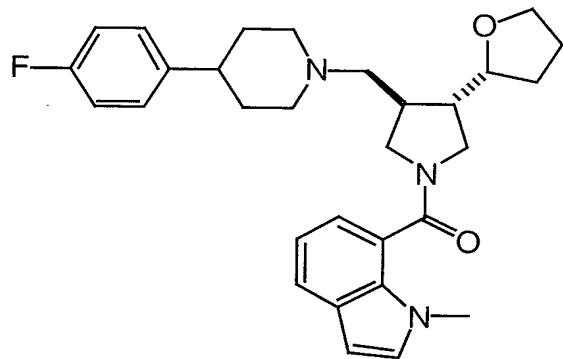
1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dithian-2-yl)pyrrolidine;



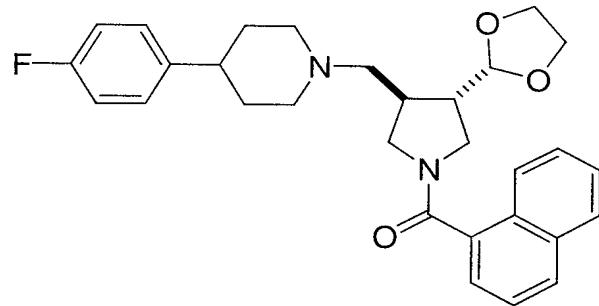
5 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-tetrahydropyranyl)pyrrolidine;



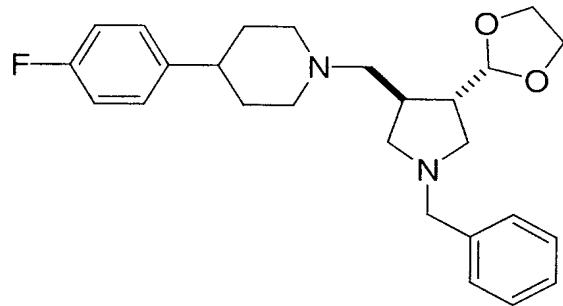
1-(1-Methyl-7-indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinyl methyl)-4-(SR)-(1,3-dithiolan-2-yl)pyrrolidine;



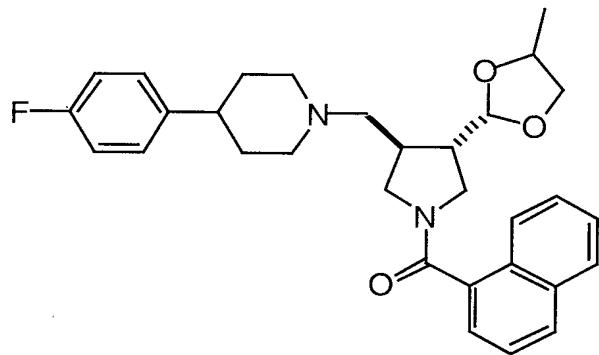
1-(1-Methyl-7-indolecarbonyl)-3-(RS)-(4-(4-fluorophenyl)piperidinyl methyl)-4-(SR)-(2-tetrahydrofuranyl)pyrrolidine;



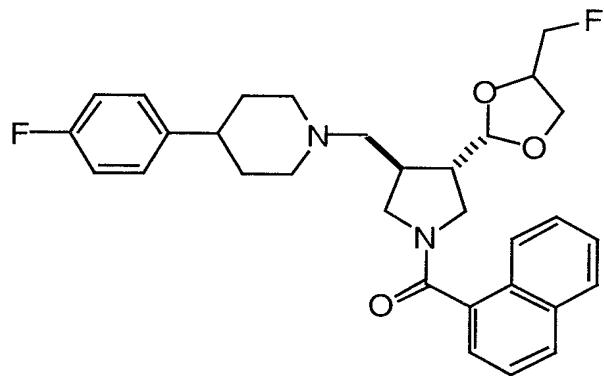
5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine;



10 1-(Benzyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine;

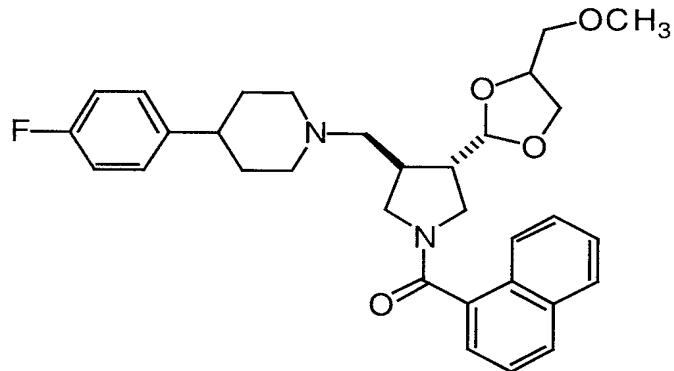


1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-methyl-1,3-dioxolan-2-yl)pyrrolidine;

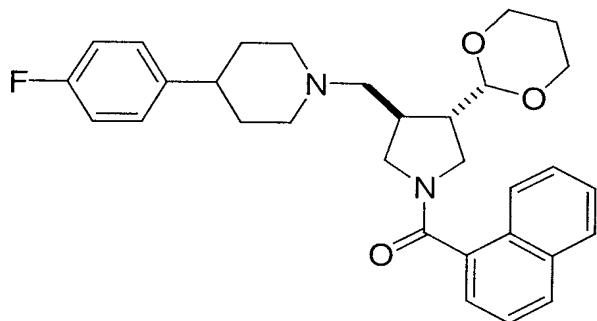


5

1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-fluoromethyl-1,3-dioxolan-2-yl)pyrrolidine;



1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-methoxymethyl-1,3-dioxolan-2-yl)pyrrolidine;



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxan-2-yl)pyrrolidine;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of modulating chemokine receptor activity in a patient in need of such modulation comprising the administration of an effective amount of the compound.

The present invention is directed to the use of the foregoing spiro-substituted azacycles as modulators of chemokine receptor activity. In particular, these compounds are useful as modulators of the chemokine receptors, including CCR-3 and/or CCR-5.

The utility of the compounds in accordance with the present invention as modulators of chemokine receptor activity may be demonstrated by methodology known in the art, such as the assay for CCR-5 binding as disclosed by Van Riper, et al., *J. Exp. Med.*, 177, 851-856 (1993), and the assay for CCR-3 binding as disclosed by Daugherty, et al., *J. Exp. Med.*, 183, 2349-2354 (1996). Cell lines for expressing the receptor of interest include those naturally expressing the receptor, such as EOL-3 or THP-1, or a cell engineered to express a recombinant receptor, such as CHO, RBL-2H3, HEK-293. For example, a CCR3 transfected AML14.3D10 cell line has been placed on restricted deposit with American Type Culture Collection in Rockville, Maryland as ATCC No. CRL-12079, on April 5, 1996. The utility of the compounds in accordance with the present invention as inhibitors of the spread of HIV infection in cells may be demonstrated by methodology known in the art, such as the HIV quantitation assay disclosed by Nunberg, et al., *J. Virology*, 65 (9), 4887-4892 (1991).

In particular, the compounds of the following examples had activity in binding to the CCR-3 or the CCR-5 receptor in the aforementioned assays, generally with an IC₅₀ of less than about 1 μ M. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

5 Mammalian chemokine receptors provide a target for interfering with or promoting eosinophil and/or lymphocyte function in a mammal, such as a human. Compounds which inhibit or promote chemokine receptor function, are particularly useful for modulating eosinophil and/or lymphocyte function for therapeutic purposes. Accordingly, the present invention is directed to compounds which are useful in the
10 prevention and/or treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic diseases, atopic conditions including allergic rhinitis, dermatitis, conjunctivitis, and asthma, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis.

15 For example, an instant compound which inhibits one or more functions of a mammalian chemokine receptor (e.g., a human chemokine receptor) may be administered to inhibit (i.e., reduce or prevent) inflammation. As a result, one or more inflammatory processes, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, is inhibited. For example, eosinophilic infiltration to inflammatory sites (e.g., in
20 asthma) can be inhibited according to the present method.

25 Similarly, an instant compound which promotes one or more functions of a mammalian chemokine receptor (e.g., a human chemokine) is administered to stimulate (induce or enhance) an inflammatory response, such as leukocyte emigration, chemotaxis, exocytosis (e.g., of enzymes, histamine) or inflammatory mediator release, resulting in the beneficial stimulation of inflammatory processes. For example, eosinophils can be recruited to combat parasitic infections.

30 In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment,

the disease or condition is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

Diseases or conditions of humans or other species which can be treated with inhibitors of chemokine receptor function, include, but are not limited to:

- 5 inflammatory or allergic diseases and conditions, including respiratory allergic diseases such as asthma, particularly bronchial asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or
- 10 ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus,
- 15 myasthenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune thyroiditis, Behcet's disease; graft rejection (e.g., in transplantation), including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as
- 20 dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinophilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs. Other diseases or conditions in which undesirable inflammatory responses are to be inhibited can be treated, including, but not limited to, reperfusion injury,
- 25 atherosclerosis, certain hematologic malignancies, cytokine-induced toxicity (e.g., septic shock, endotoxic shock), polymyositis, dermatomyositis.

Diseases or conditions of humans or other species which can be treated with promoters of chemokine receptor function, include, but are not limited to:

immunosuppression, such as that in individuals with immunodeficiency syndromes

- 30 such as AIDS, individuals undergoing radiation therapy, chemotherapy, therapy for autoimmune disease or other drug therapy (e.g., corticosteroid therapy), which causes immunosuppression; immunosuppression due congenital deficiency in receptor function or other causes; and infectious diseases, such as parasitic diseases, including, but not limited to helminth infections, such as nematodes (round worms);
- 35 (Trichuriasis, Enterobiasis, Ascariasis, Hookworm, Strongyloidiasis, Trichinosis,

filariasis); trematodes (flukes) (Schistosomiasis, Clonorchiasis), cestodes (tape worms) (Echinococcosis, Taeniasis saginata, Cysticercosis); visceral worms, visceral larva migrans (e.g., Toxocara), eosinophilic gastroenteritis (e.g., *Anisaki* spp., *Phocanema* spp.), cutaneous larva migrans (*Ancylostoma braziliense*, *Ancylostoma caninum*).

5 The compounds of the present invention are accordingly useful in the prevention and treatment of a wide variety of inflammatory and immunoregulatory disorders and diseases, allergic conditions, atopic conditions, as well as autoimmune pathologies.

10 In another aspect, the instant invention may be used to evaluate putative specific agonists or antagonists of chemokine receptors, including CCR-3 and/or CCR-5. Accordingly, the present invention is directed to the use of these compounds in the preparation and execution of screening assays for compounds which modulate the activity of chemokine receptors. For example, the compounds of 15 this invention are useful for isolating receptor mutants, which are excellent screening tools for more potent compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other compounds to chemokine receptors, e.g., by competitive inhibition. The compounds of the instant invention are also useful for the evaluation of putative specific modulators of the 20 chemokine receptors, including CCR-3 and/or CCR-5. As appreciated in the art, thorough evaluation of specific agonists and antagonists of the above chemokine receptors has been hampered by the lack of availability of non-peptidyl (metabolically resistant) compounds with high binding affinity for these receptors. Thus the compounds of this invention are commercial products to be sold for these purposes.

25 The present invention is further directed to a method for the manufacture of a medicament for modulating chemokine receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

30 The present invention is further directed to the use of these compounds in the prevention or treatment of infection by a retrovirus, in particular, the human immunodeficiency virus (HIV) and the treatment of, and delaying of the onset of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both 35 symptomatic and asymptomatic, and actual or potential exposure to HIV. For

example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, organ transplant, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

5 In a preferred aspect of the present invention, a subject compound may be used in a method of inhibiting the binding of a chemokine to a chemokine receptor, such as CCR-3 or CCR-5, of a target cell, which comprises contacting the target cell with an amount of the compound which is effective at inhibiting the binding of the chemokine to the chemokine receptor.

10 The subject treated in the methods above is a mammal, preferably a human being, male or female, in whom modulation of chemokine receptor activity is desired. "Modulation" as used herein is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism. In a preferred aspect of the present invention, modulation refers to antagonism of chemokine receptor activity. The term 15 "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

20 The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified 25 ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

25 The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

30 Combined therapy to modulate chemokine receptor activity and thereby prevent and treat inflammatory and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as 35 rheumatoid arthritis and atherosclerosis, and those pathologies noted above is illustrated by the combination of the compounds of this invention and other compounds which are known for such utilities.

35 For example, in the treatment or prevention of inflammation, the present compounds may be used in conjunction with an antiinflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-

lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroid analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextromethorphan; a diuretic; and a sedating or non-sedating antihistamine. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention. Examples of other active ingredients that may be combined with a compound of the present invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) VLA-4 antagonists such as those described in US 5,510,332, WO95/15973, WO96/01644, WO96/06108, WO96/20216, WO96/22966, WO96/31206, WO96/40781, WO97/03094, WO97/02289, WO 98/42656, WO98/53814, WO98/53817, WO98/53818, WO98/54207, and WO98/58902; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleannamine, hydroxyzine, methdilazine,

promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, and 5 pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, 10 fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpina, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives 15 (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) 20 inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CCR-1, CCR-2, CCR-3 and CCR-5; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, 25 fenofibrate and benzofibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone and pioglitazone); (l) preparations of interferon beta (interferon beta-1 α , interferon beta-1 β); (m) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of 30 the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of 35 the compound of the present invention to the NSAID will generally range from about

1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

5 The present invention is further directed to combinations of the present compounds with one or more agents useful in the prevention or treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or 10 vaccines known to those of ordinary skill in the art.

ANTIVIRALS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
141 W94	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
1592U89	Glaxo Wellcome	HIV infection, AIDS, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC

Adefovir dipivoxil	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL
Alpha Interferon	Glaxo Wellcome	HIV positive, AIDS Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon	Erbamont (Stamford, CT)	
AR177	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
beta-fluoro-ddA	Aronex Pharm	HIV infection, AIDS, ARC
(-) 6-Chloro-4(S)- cyclopropylethynyl- 4(S)-trifluoro-methyl- 1,4-dihydro-2H-3,1- benzoxazin-2-one	Nat'l Cancer Institute Merck	AIDS-associated diseases HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	sight threatening CMV
Ganciclovir		peripheral CMV retinitis
Delavirdine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (protease inhibitor)

Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC	Hoffman-La Roche	HIV infection, AIDS, ARC
Dideoxycytidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
ddI		
Dideoxyinosine		
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Efavirenz, DMP-266	DuPont-Merck Pharmaceuticals	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GW 141	Glaxo Welcome	HIV infection, AIDS, ARC (protease inhibitor)
GW 1592	Glaxo Welcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)

HB Y097	Hoechst Marion Roussel	HIV infection, AIDS, ARC
Hypericin	VIMRx Pharm.	(non-nucleoside reverse transcriptase inhibitor) HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC
Nevirapine	Boehringer Ingelheim	(protease inhibitor) HIV infection, AIDS, ARC
Novapren	Novaferon Labs, Inc. (Akron, OH)	(protease inhibitor) HIV inhibitor
Peptide T	Peninsula Labs	AIDS
Octapeptide Sequence	(Belmont, CA)	

Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy- thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole	Viratek/ICN	asymptomatic HIV
Ribavirin	(Costa Mesa, CA)	positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNO-MODULATORS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte	Genetics Institute	AIDS
Macrophage Colony Stimulating Factor	Sandoz	
Granulocyte	Hoeschst-Roussel	AIDS
Macrophage Colony Stimulating Factor	Immunex	
Granulocyte	Schering-Plough	AIDS, combination w/AZT
Macrophage Colony Stimulating Factor		
HIV Core Particle	Rorer	seropositive HIV
Immunostimulant		
IL-2	Cetus	AIDS, in combination w/AZT
Interleukin-2		
IL-2	Hoffman-La Roche	AIDS, ARC, HIV, in combination w/AZT
Interleukin-2	Immunex	
IL-2	Chiron	AIDS, increase in CD4 cell counts
Interleukin-2 (aldeslukin)		

Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE	Ciba-Geigy Corp.	Kaposi's sarcoma
Muramyl-Tripeptide		
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4	Genentech	AIDS, ARC
Recombinant Soluble Human CD4		
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528	Smith Kline	HIV infection
Soluble T4		
Thymopentin	Immunobiology Research Institute	HIV infection

Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon
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ANTI-INFECTIVES

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis prevention of oral candidiasis
Pastille	Squibb Corp.	
Nystatin Pastille		
Ornidyl	Merrell Dow	PCP
Eflornithine		
Pentamidine	LyphoMed	PCP treatment
Isethionate (IM & IV)	(Rosemont, IL)	
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine isethionate for inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma

Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection
Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as

5 AZT, 3TC, ddC or ddI. Preferred agents for combination therapy include: Zidovudine, Lamivudine, Stavudine, Efavirenz, Ritonavir, Nelfinavir, Abacavir, Indinavir, 141-W94 (4-amino-N-((2 syn,3S)-2-hydroxy-4-phenyl-3-((S)-tetrahydrofuran-3-yloxy carbonyl amino)-butyl)-N-isobutyl-benzenesulfonamide), N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(2-

10 benzo[b]furanyl methyl)-2(S)-N'-(t-butylcarbox-amido)-piperazinyl))-pentaneamide, and Delavirdine. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarbo-xamido)-piperazinyl))-pentane-amide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally

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administered at a dosage of 800 mg three times a day. Other preferred inhibitors of HIV protease include nelfinavir and ritonavir. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, which may be prepared by methods disclosed in EP 0,582,455. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations with the compounds of the present invention include the following: (1) Zidovudine and Lamivudine; (2) Stavudine and Lamivudine; (3) Efavirenz; (4) Ritoavir; (5) Nelfinavir; (6) Abacavir; (7) Indinavir; (8) 141-W94; and (9) Delavirdine. Preferred combinations with the compounds of the present invention further include the following (1) indinavir, with efavirenz or (-) 6-chloro-4(S)-cyclopropylethynyl-4(S)-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In

the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which

5 results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, 10 or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the 15 active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or 20 acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as 25 glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules 30 wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, 35 hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum

tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example

- 5 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,
- 10 for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

- 20 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.
- 25

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example

- 30 gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile

5 injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane
10 diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

15 The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and
20 polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of The present invention are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

25 The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or
30 multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active

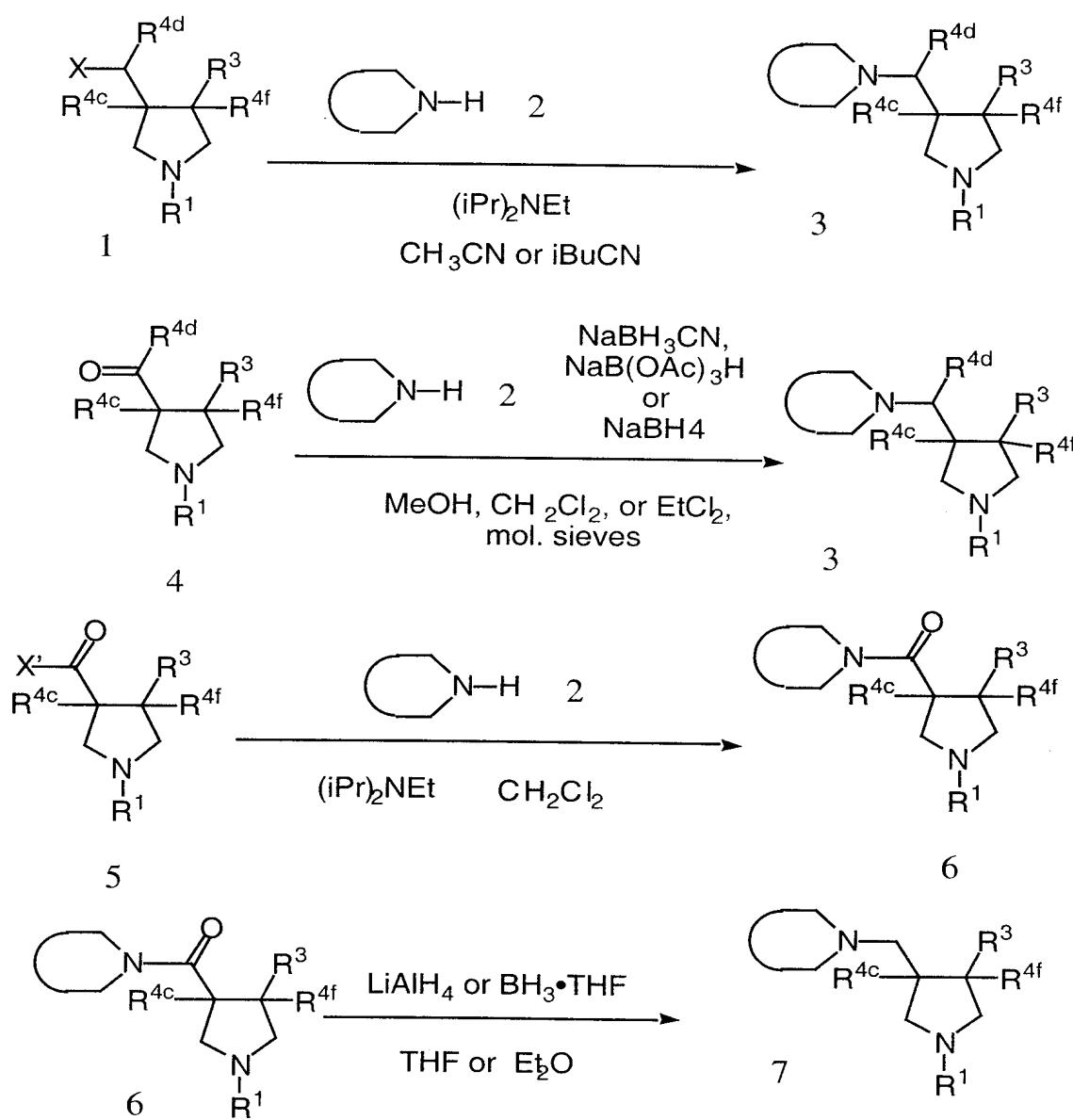
ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, 5 preferably once or twice per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, 10 general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made from known procedures or as illustrated.

15 Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples.

SCHEME 1



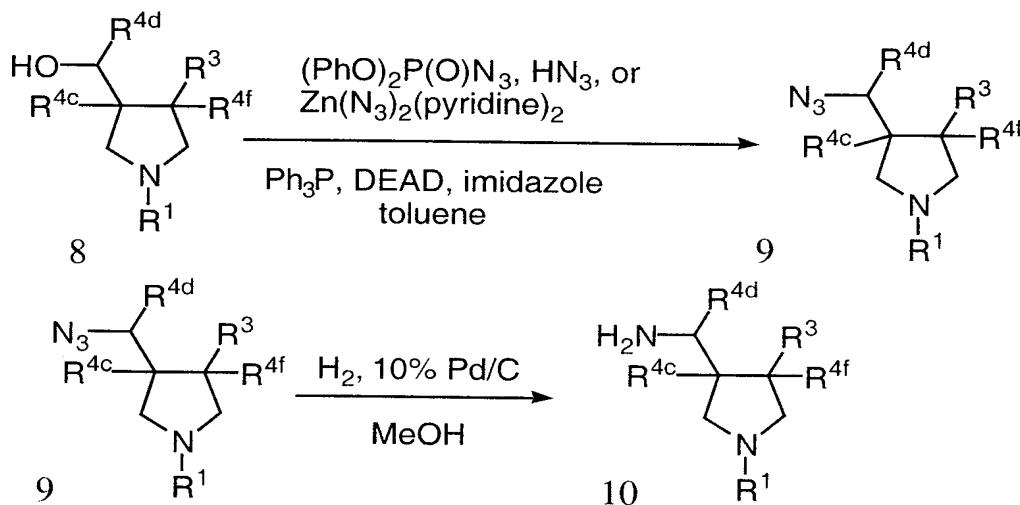
In one protocol, the compounds of the present invention are prepared by alkylating heterocycle 1 (wherein X is a leaving group such as, for example, bromide, iodide, methanesulfonate, p-toluenesulfonate, trifluoromethanesulfonate) with cyclic amine 2 under appropriate conditions to provide compound 3. Cyclic amine 2 is available commercially or can be prepared using the methods given below.

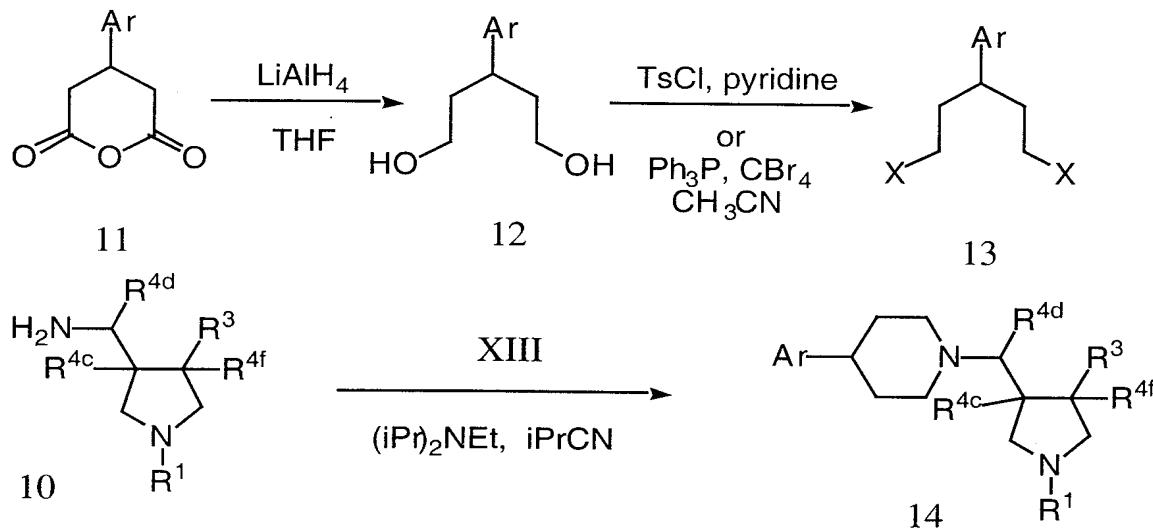
Alternatively, heterocycle 4, bearing a carbonyl group, can be combined with the cyclic amine 2 and the intermediate imine or iminium species is reduced to tertiary amine 3 under homogenous conditions (e.g. using sodium cyanoborohydride, sodium borohydride, or sodium triacetoxyborohydride) or in the presence of hydrogen and a heterogeneous catalyst (e.g. palladium on carbon or Raney nickel).

In an alternative embodiment of the present invention, heterocycle 5, bearing an activated acyl side chain (wherein X', for example, is a chloride or bromide atom, or is a hydroxybenzotriazole residue from activation of the corresponding carboxylic acid with HOBT in the presence of a suitable carbodiimide) is allowed to react with cyclic amine 2 to provide the corresponding tertiary amide 6. Compound 6 can then be treated with a suitable reducing agent (e.g. diborane; borane in THF; borane dimethylsulfide, or lithium aluminum hydride) to provide the desired product 7.

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SCHEME 2

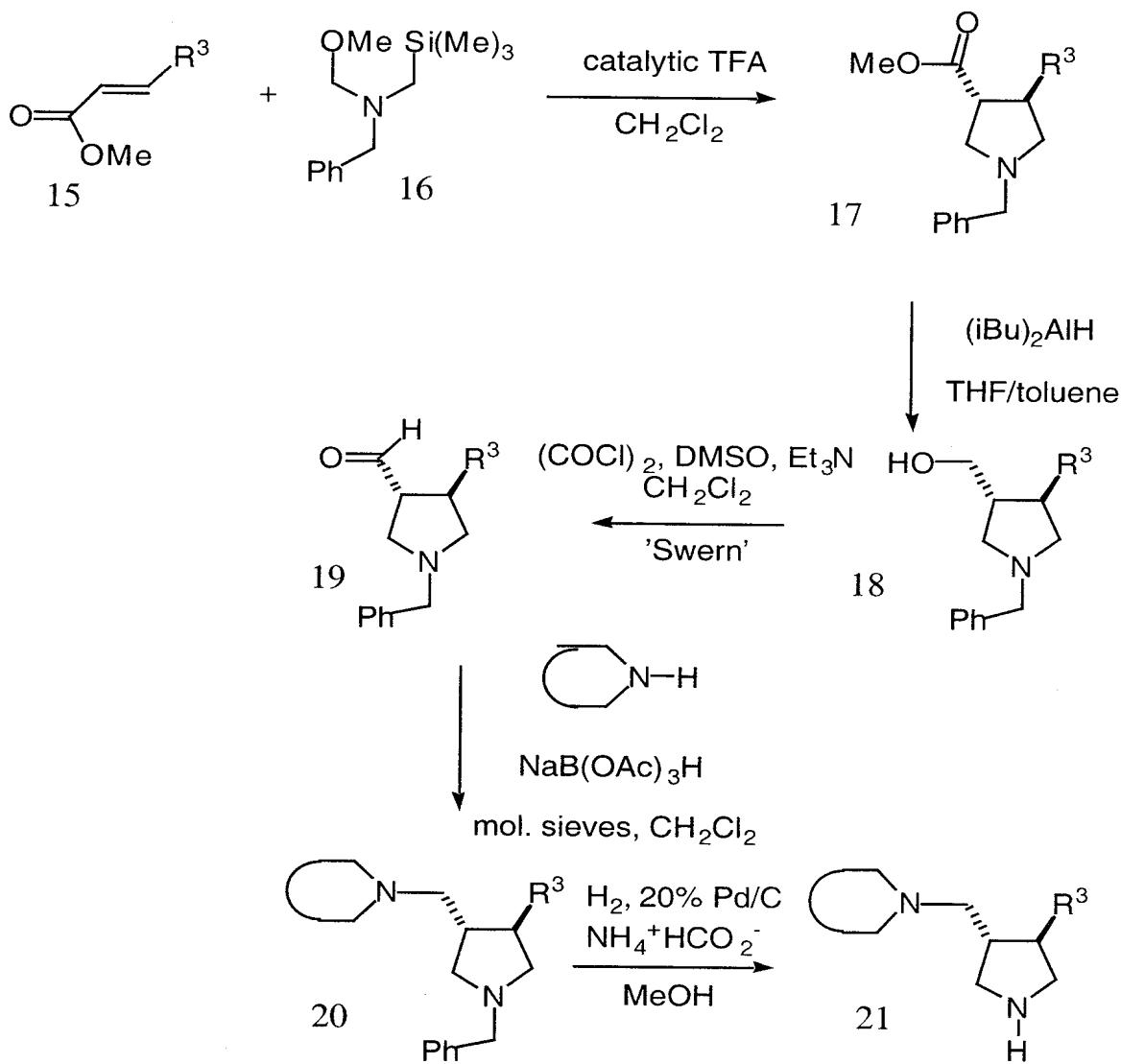




An alternative preparation of the target compounds is carried out as
 5 shown in Scheme 2. Treatment of alcohol 8 with zinc azide bis(pyridine) complex in
 the presence of triphenylphosphine and diethyl azodicarboxylate, or with
 diphenylphosphoryl azide, or with hydrazoic acid, provides azide 9. Reduction of 9,
 for example, with hydrogen and palladium on carbon, affords primary amine 10. This
 10 amine can be doubly alkylated with a bis-electrophile such as 13 under basic
 conditions, to provide the compound 14. Bis-electrophiles can be prepared from
 substituted glutaric anhydride derivatives such as 11 by reduction to diol 12 followed
 by double activation, using, for example, p-toluenesulfonyl chloride in pyridine, or
 triphenylphosphine carbon tetrabromide in acetonitrile, to provide 13 (where X = Br
 or OTs).

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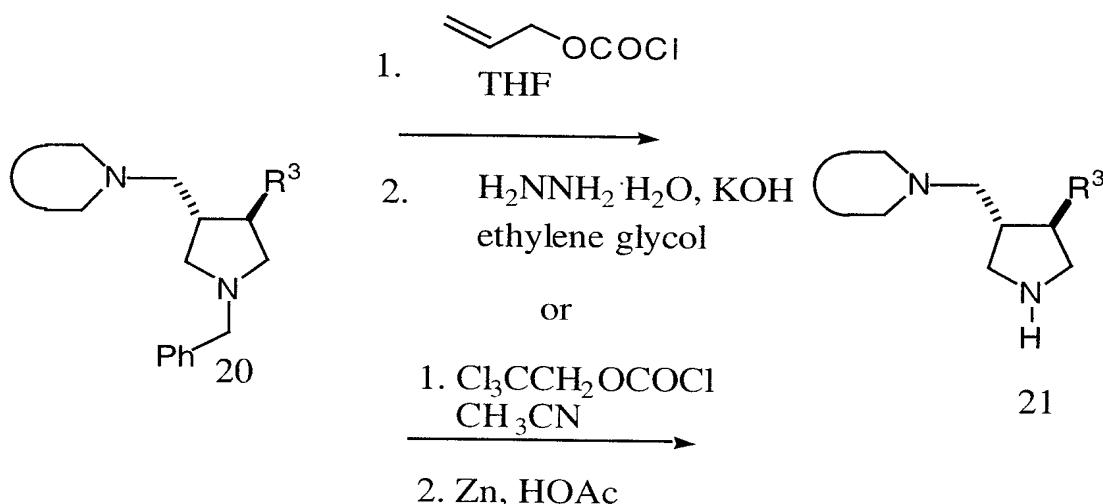
SCHEME 3



The preparation of compounds within the scope of the instant
 5 invention which bear a 1,3,4-trisubstituted pyrrolidine framework is detailed in
 Scheme 3. Treatment of a trans-cinnamic ester such as 15 with N-benzyl-N-
 methoxymethyl-N-(trimethylsilyl)-methylamine (16) in the presence of a catalytic
 amount of an acid such as TFA, titanium tetrafluoride lithium fluoride or cesium
 fluoride according to the procedure of Padwa et al (*J. Org. Chem.* **1987**, *52*, 235)
 10 preferentially affords the 3,4-trans pyrrolidine 17. Executing this sequence starting

from the cis-cinnamic ester results in preferential formation of the 3,4-cis pyrrolidine. Reduction of ester 17 with diisobutylaluminum hydride, lithium aluminium hydride, or sodium bis(2-methoxyethoxy)aluminum hydride, provides the primary alcohol 18. Oxidation of 18 to the aldehyde 19 can be carried out under numerous conditions, 5 such as with the Swern reaction, with DMSO and oxalyl chloride at low temperature, followed by triethylamine, or with various chromium trioxide-based reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1167-1171 (1992)). Reductive amination with cyclic amine 2 provides diamine 10 20. Alternatively, The N-benzyl group is cleaved in a hydrogen atmosphere in the presence of 10% palladium on carbon or with Pearlmans' catalyst [Pd(OH)₂/C] to provide the secondary amine 21.

SCHEME 4

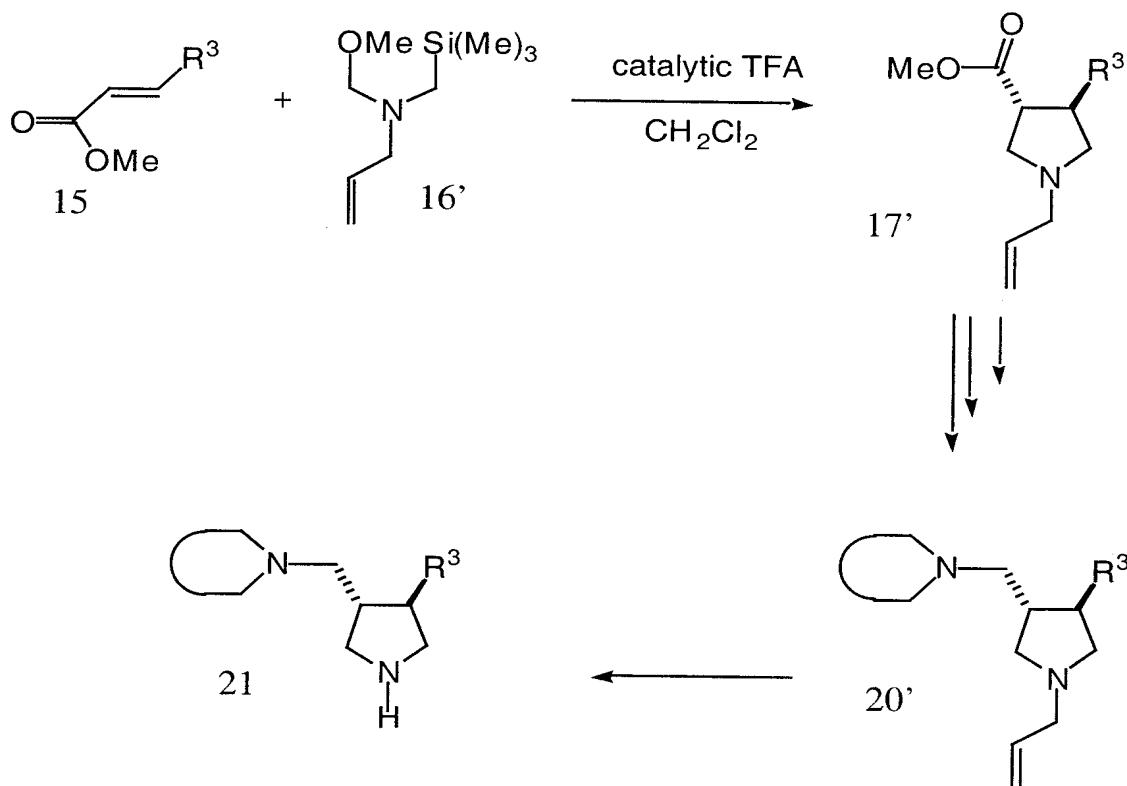


15 In cases when certain substituents are labile to hydrogenolysis conditions, alternative methods to remove the benzyl group of compound 20 are described in Scheme 4. Compound 20 may be converted to the allyloxycarbamate derivative by stirring with allylchloroformate at rt in a solvent such as THF (T. Shono, Y. Matsumura, *J. Org. Chem.*, **1984**, *48*, 300). Subsequent reaction with hydrazine hydrate and KOH in 20 ethylene glycol at elevated temperatures provides the amine 21. Compound 20 may also be converted to its 2,2,2,-trichloroethyloxycarbamate derivative by stirring with 2,2,2-trichloroethylchloroformate in a solvent such as acetonitrile (V. H. Rawal, R. J. Jones, *J. Org. Chem.*, **1987**, *52*, 19). This derivative is then converted to amine 21 by

reaction with zinc powder in acetic acid at slightly elevated temperatures such as at 40 °C.

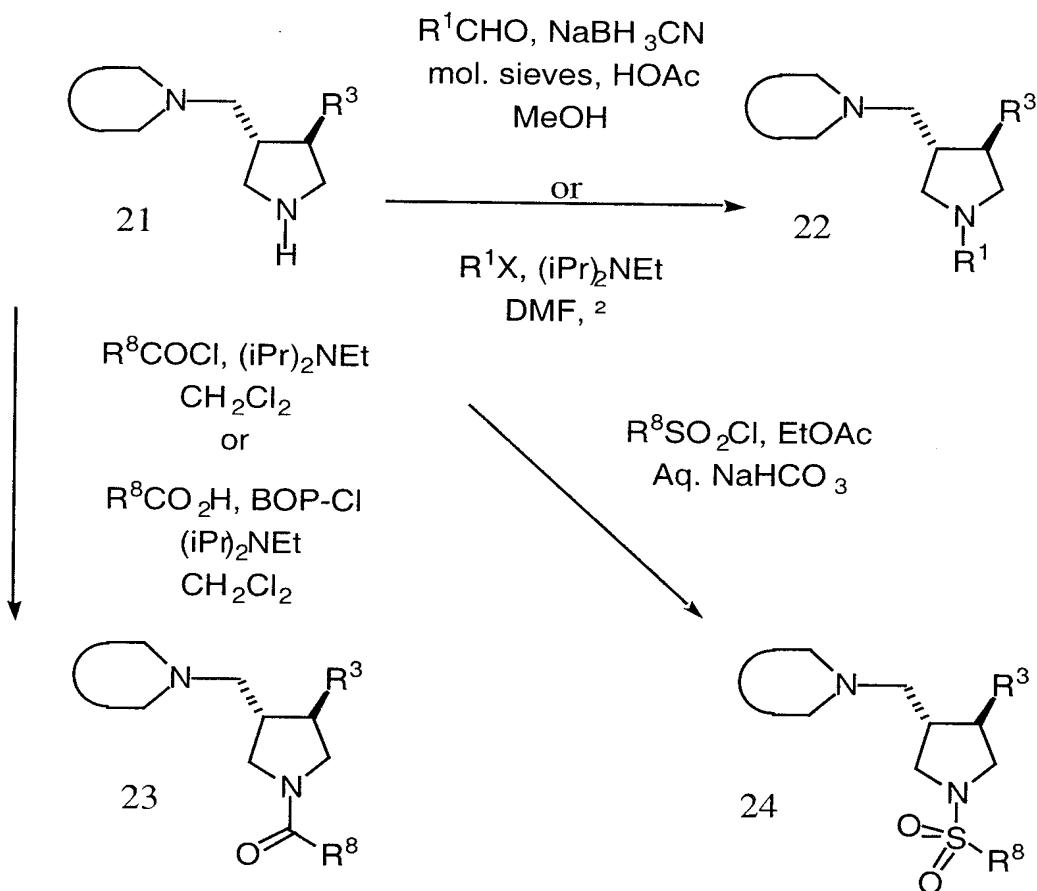
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SCHEME 5

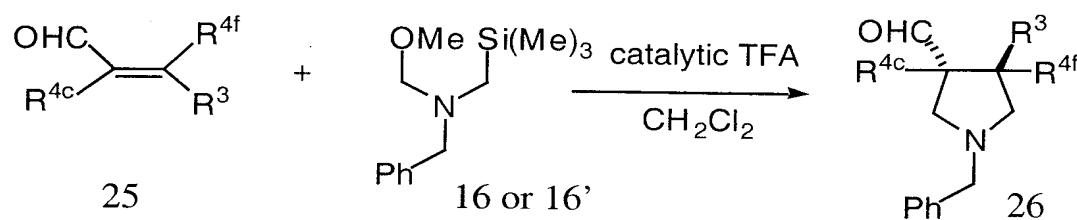


Scheme 5 describes a modification of Scheme 3 when substituents are not compatible with hydrogenolysis of the benzyl group of compound 20. In this variation, treatment of a trans-cinnamic ester 15 with N-allyl-N-methoxymethyl-N-(trimethylsilyl)-methylamine (16') according to procedures described in Scheme 3 provides N-allylpiperazine derivative 17'. The reagent N-allyl-N-methoxymethyl-N-(trimethylsilyl)-methylamine is prepared after procedures described by Padwa et al (*J. Org. Chem.* **1985**, *50*, 4006 and *J. Org. Chem.* **1987**, *52*, 235). Subsequent elaboration as described in Scheme 3 gives compound 20'. The allyl group of compound 20' is removed by heating with Wilkinson's catalyst ([Rh(PPh₃)₃Cl]) in a solvent such as 85% CH₃CN in water.

SCHEME 6

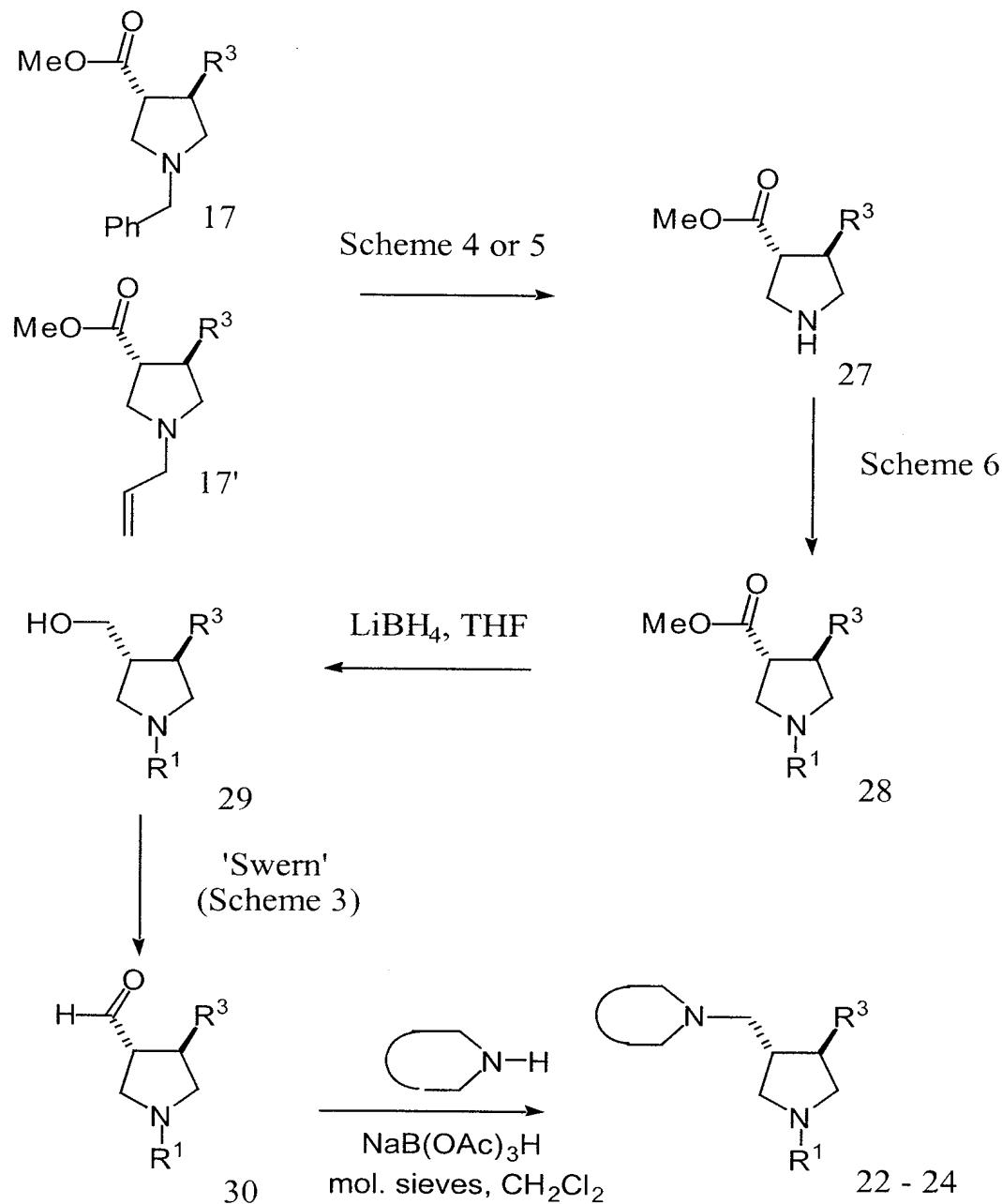


The unsubstituted pyrrolidine 21 may be further functionalized as shown in Scheme 6. Reductive amination with suitable aldehydes under standard conditions provides the tertiary amine 22. The pyrrolidine nitrogen may be alkylated with a suitable halide, methanesulfonate, p-toluenesulfonate, etc. carried out under standard conditions to provide N-alkylated pyrrolidine 22. Alternatively, compound 22 is acylated with, for example, acid chlorides or bromides, or activated esters utilizing a variety of the standard coupling conditions to give amide 23. For example, reaction of compound 22 and a carboxylic acid with BOP-Cl and triethylamine in a solvent such as methylene chloride is a commonly used procedure. The sulfonamide 24 is prepared under standard conditions by exposing 21 to an alkyl or aryl sulfonyl chloride in the presence of a suitable base to neutralize the formed hydrogen chloride.

SCHEME 7

Compounds possessing geminal substituents on positions 3 or 4 (or on both C3 and C4) of the pyrrolidine ring are prepared by the method shown in Scheme 5. Cycloaddition of unsaturated aldehyde 25 with reagent 16 or 16' as described in Schemes 3 or 5 provides pyrrolidine aldehyde 26. Further elaboration of 26 can be achieved as described in the previous Schemes.

SCHEME 8

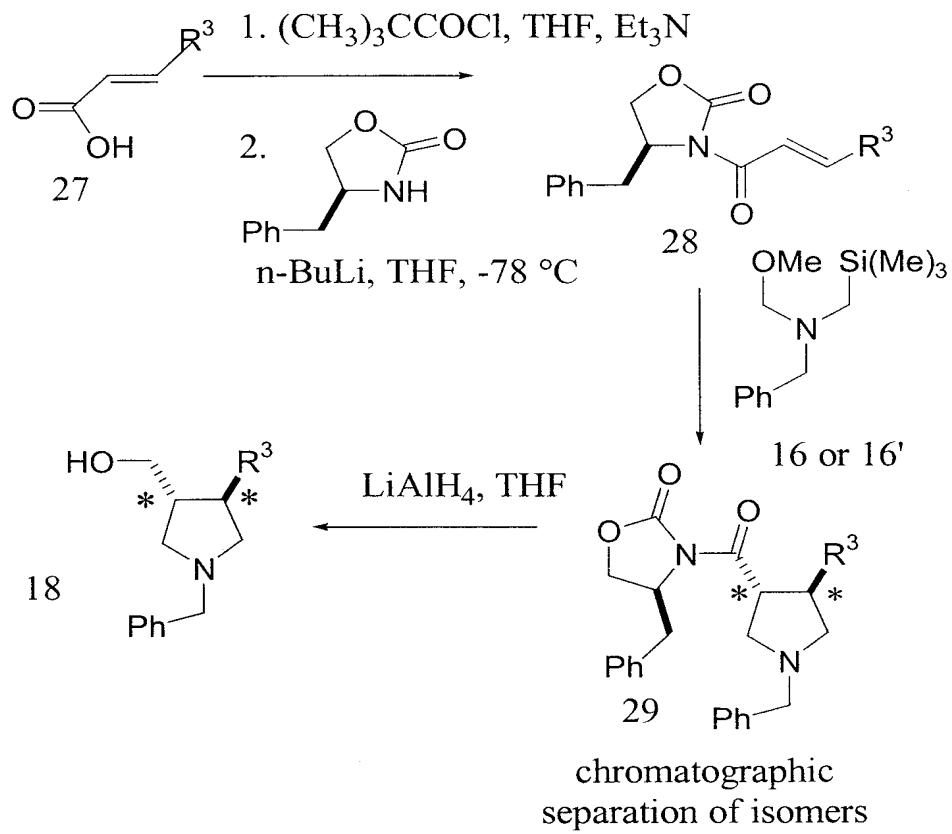


An alternative approach to the synthesis of chemokine modulators is described in Example 8. Ester derivatives 17 (Scheme 3) or 17' (Scheme 5) are first 5 debenzylated or deallylated by procedures described in Schemes 3, 4 or 5 to give

secondary amine derivative 27. Compound 27 can then be elaborated as described in Scheme 6 to provide compound 28. The ester group of 28 can be selectively reduced with a reagent such as lithium borohydride in THF to give the alcohol 29 which is then converted to aldehyde 30 under Swern conditions as described in Scheme 3.

5 Aldehyde 39 is then converted to derivative 22 (or 23 or 24) by reductive amination (Scheme 3).

SCHEME 9



10 The preparation of optically active compounds described in Scheme 9 follows procedures described by Ma et.al., (*Tetrahedron: Assymmetry* **1997**, *8*, 883). Reaction of a trans-acrylic acid with oxalyl chloride or pivaloyl chloride and triethylamine in THF provide the mixed anhydride intermediate. This is then treated with the lithium salt of an appropriate chiral auxiliary such as (S)-benzyl-2-oxazolidinone in THF at reduced temperatures, such as -78 °C to give amide 28.

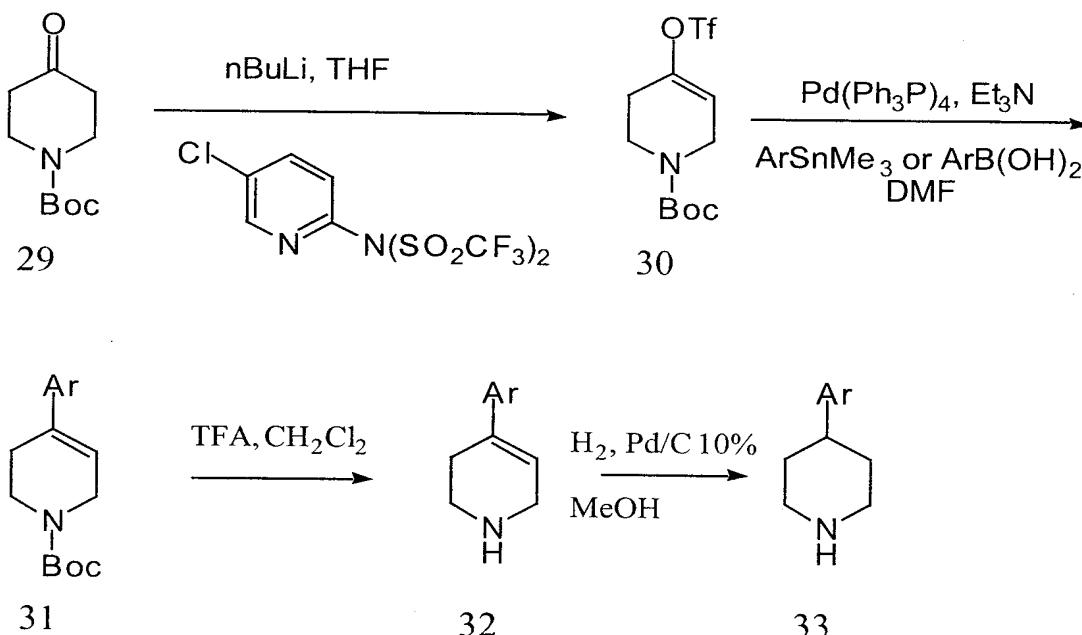
15 This acrylamide is then reacted with N-benzyl-N-methoxymethyl-N-(trimethylsilyl)-methylamine (16) or N-allyl-N-methoxymethyl-N-(trimethylsilyl)-methylamine (16')

as described in Schemes 3 and 5, respectively, to give pyrrolidine intermediate 29 or the corresponding N-allyl derivative. Modest diastereoselectivity is achieved in these cyclizations as shown by Ma et al. However, the separate optically active isomers may be easily obtained by simple chromatography on silica gel. Reaction of the 5 selected diastereomer 29 with LiAlH₄ in THF at 0 °C provides the optically active version of compound 18 which is further elaborated as described in the previous Schemes

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The various piperidine derivatives, when not commercially available, are prepared as described in the following Schemes.

SCHEME 10

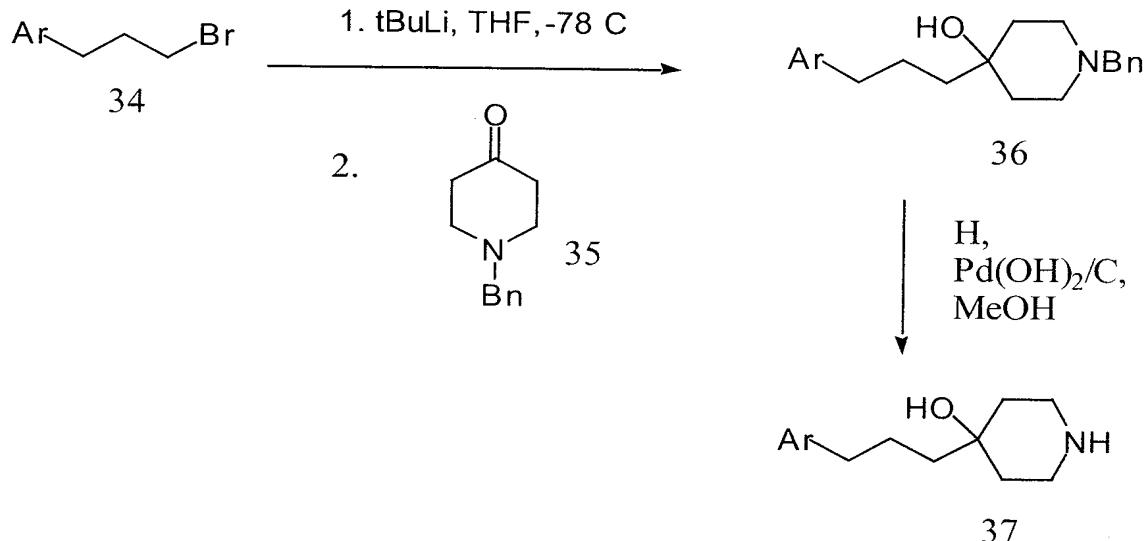


The synthesis of 4-arylpiperidine groups is presented in Scheme 10. Enolate formation of the 4-piperidone derivative 29 followed by formation of the 15 vinyl triflate with either 2-[N,N-bis(trifluoromethyl sulfonyl)amino]-5-chloropyridine or with N-phenyltriflimide provides triflate ether 30. Palladium-mediated coupling with a suitable aryl stannane or aryl boronic acid provides the tetrahydropyridine derivative 31. The Boc protecting group can be removed with TFA to give amine 32 which is then hydrogenated under standard conditions to give piperidine 33. 20 Alternatively, tetrahydropyridine derivative 31 is first hydrogenated and then

deprotected. Modification of the aryl group of compound 31 or 33 is achieved using appropriate chemical modification schemes.

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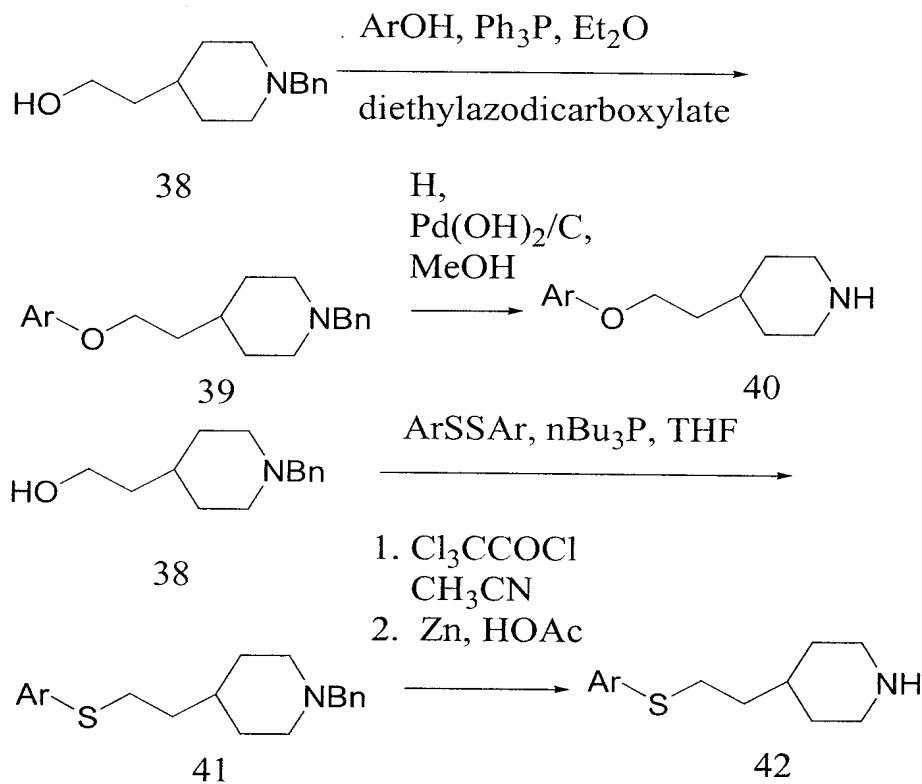
SCHEME 11



A method of preparing 4-(3-aryl-1-propyl)-4-hydroxypiperidine derivatives is described in Scheme 11. A suitable 3-arylpropyl halide 34 in THF at - 10 78 °C is reacted with a base such as t-butyl lithium. This is then reacted with a 15 protected 4-piperidone derivative such as N-benzyl-4-piperidone 35 to give the arylpropylpiperidine derivative 36. Deprotection by hydrogenation with Pd(OH)₂/C (Pearlman's catalyst) gives piperidine derivative 37 which can be reacted with compound 19 as described in Scheme 3.

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SCHEME 12

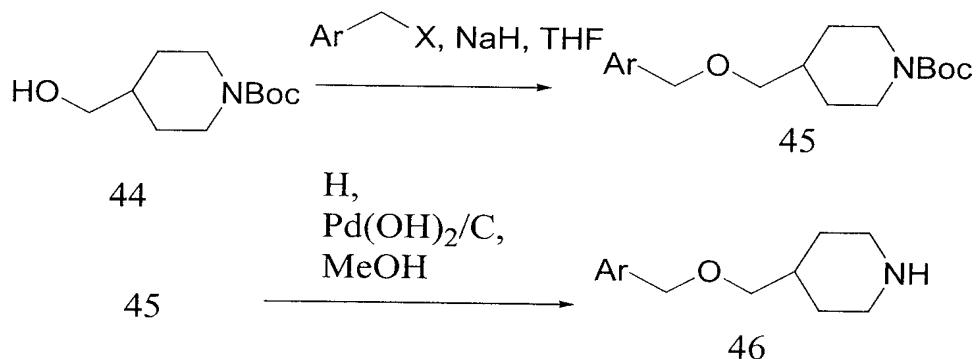


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A method of preparing 4-aryloxyethylpiperidine derivatives is described in Scheme 12. Reaction of commercially available N-benzyl-4-hydroxyethylpiperidine with an appropriate aryl alcohol under standard Mitsunobu conditions, followed by deprotection gives the corresponding piperidine derivative. The corresponding mercapto derivative is prepared by reaction of compound 38 with an aryl disulfide and tri-n-butylphosphine in THF with heating at reflux to give compound 41. Compound 41 is then converted to compound 42 as described in Scheme 4.

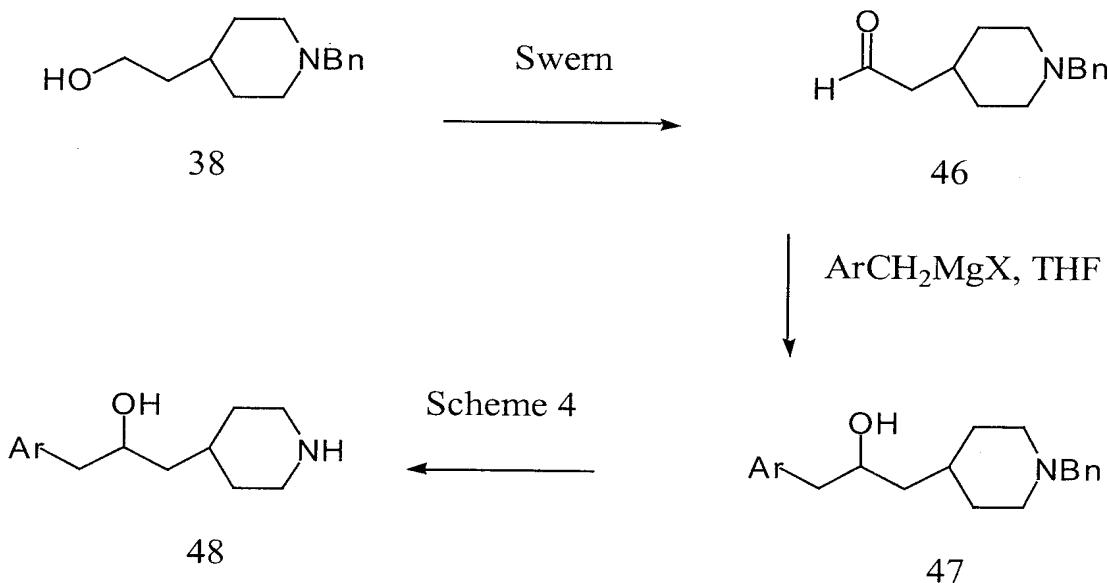
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SCHEME 13



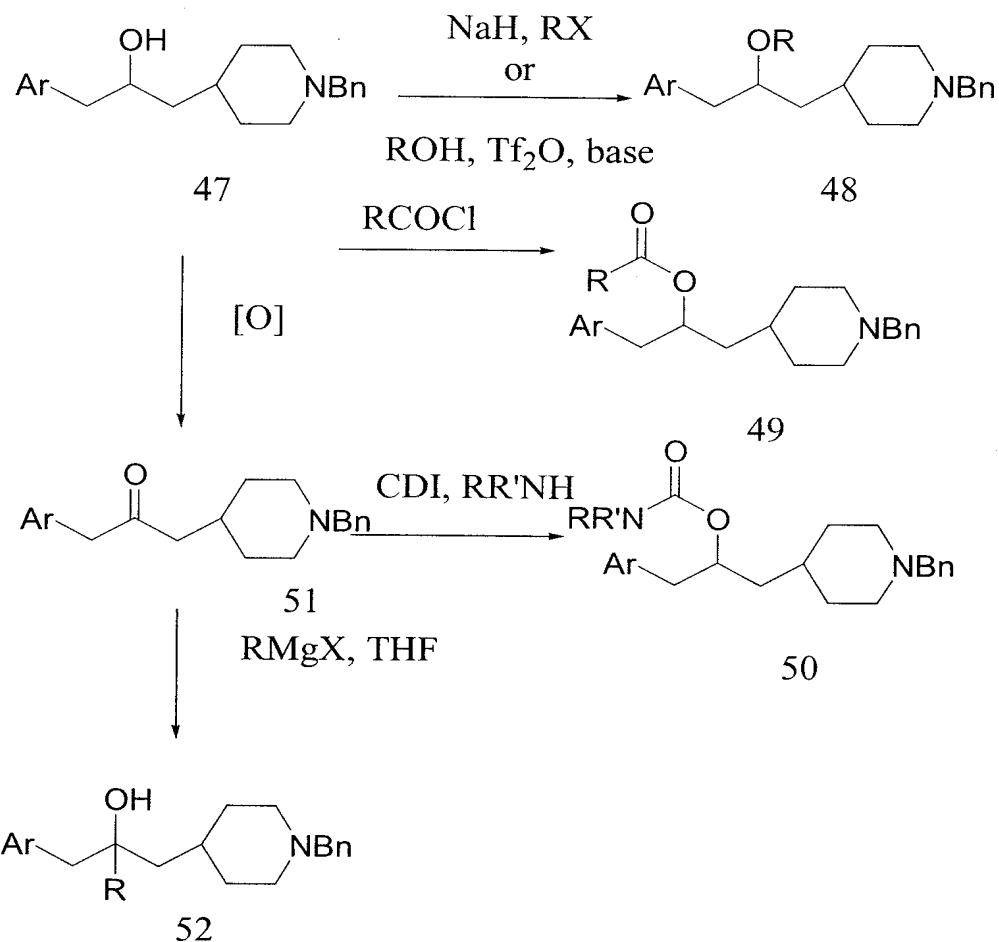
5 Compound 45 can be prepared (Scheme 13) by alkylation of compound 44 (prepared from isonipecotic acid) with an arylmethylhalide, bromide, iodide, methanesulfonate, p-toluenesulfonate, or trifluoromethanesulfonate in a solvent such as THF with a base such as sodium hydride. Subsequently, compound 45 is deprotected by reaction with trifluoroacetic acid in a solvent such as methylene 10 chloride to give compound 46.

SCHEME 14



In Scheme 14, the preparation of 4-(3-aryl-2-hydroxypropyl) piperidines is described. Compound 38 is converted to aldehyde 46 by the Swern-type conditions (oxalyl chloride, DMSO, Et₃N). Reaction of compound 46 with Grignard reagents or other related nucleophiles gives hydroxy derivative 47. Compound 47 is then converted to piperidine 48 by procedures described in Scheme 4.

SCHEME 15



5 Compound 47 can be further derivatized as depicted in Scheme 15.
Ether derivatives 48 can be prepared by reaction with an alkylhalide, tosylate or
triflate in the presence of a base such as sodium hydride in an aprotic inert solvent
such as THF. Alternatively, an excess of silver oxide (Ag_2O) is used in place of the
base. In an alternate procedure, reaction of an alcohol with trifluoromethane sulfonic
10 anhydride (Tf_2O , triflic anhydride) in dichloromethane at reduced temperature,
preferably -78°C gives the preformed triflate. To this solution is added compound 47,
the reaction mixture is warmed to room temperature and stirring is continued until
reaction is complete.

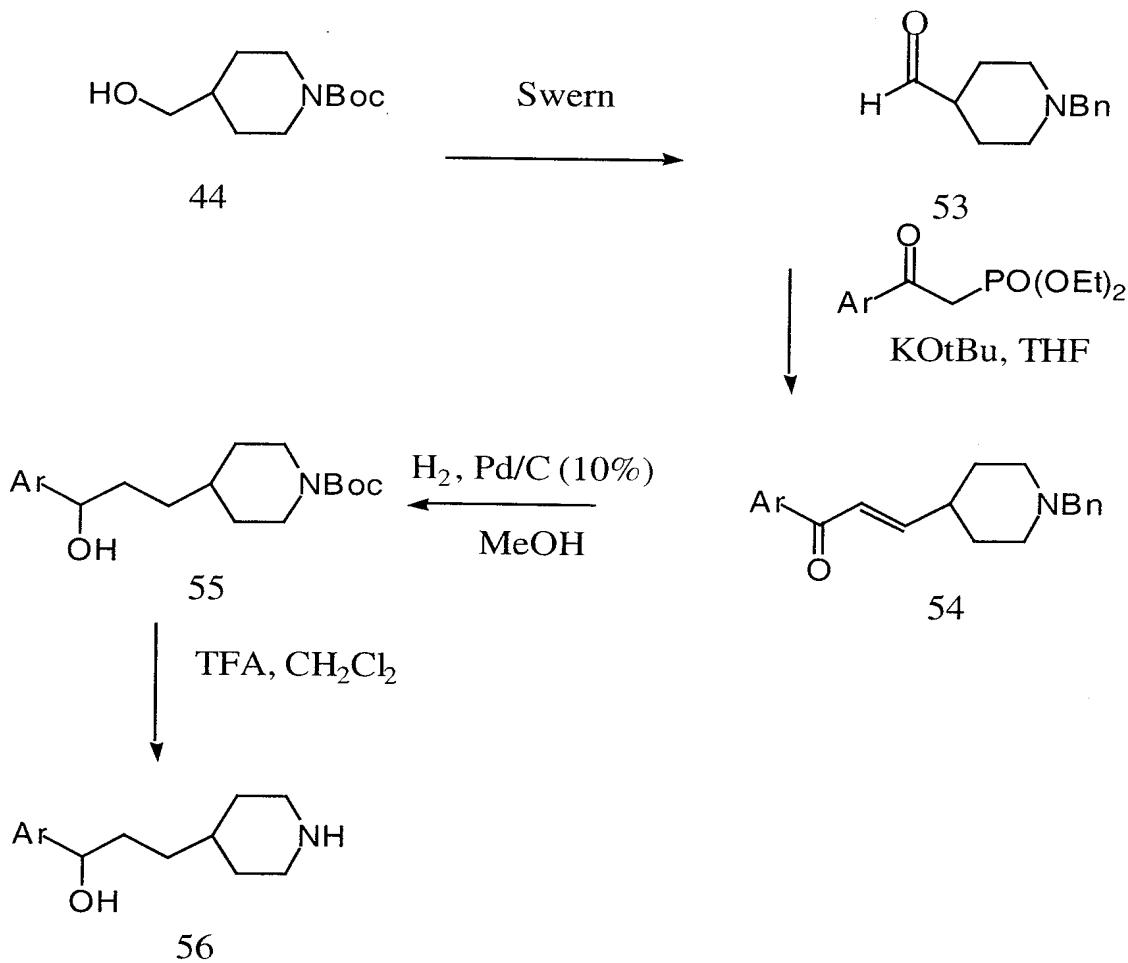
15 Esters (compound 49) can be prepared by reaction of a pre-formed carboxylic acid chloride with compound 47 in a basic solvent such as pyridine or

triethylamine. The acid chlorides, when not purchased, are prepared by stirring the carboxylic acids in reagents such as oxalyl chloride or thionyl chloride. C4 sulfonate derivatives are prepared in a similar manner by reaction with sulfonyl chlorides.

C4 carbamate and carbonate derivatives (compound 52) are prepared
5 by first reacting compound 47 with carbonyldiimidazole (CDI) to obtain the imidazolecarbonyl intermediate which is then reacted with an amine (R^1R^2NH) or an alcohol to give the corresponding carbonate or carbamate derivatives.

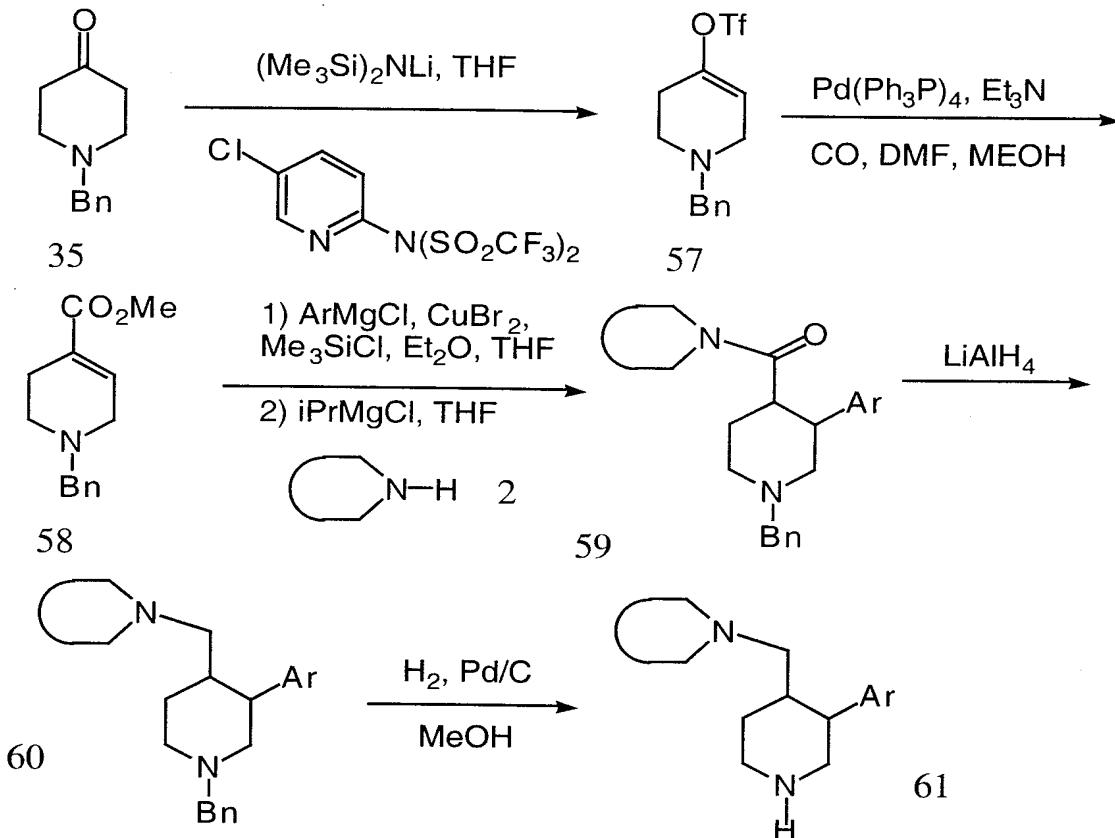
Compound 47 can be oxidized to the corresponding ketone 51 by any number of standard conditions. It can then be reaction with Grignard reagents or
10 related nucleophiles (as in Scheme 14) to give the tertiary hydroxy derivative 52. This alcohol can then be further modified as described in this scheme.

SCHEME 16



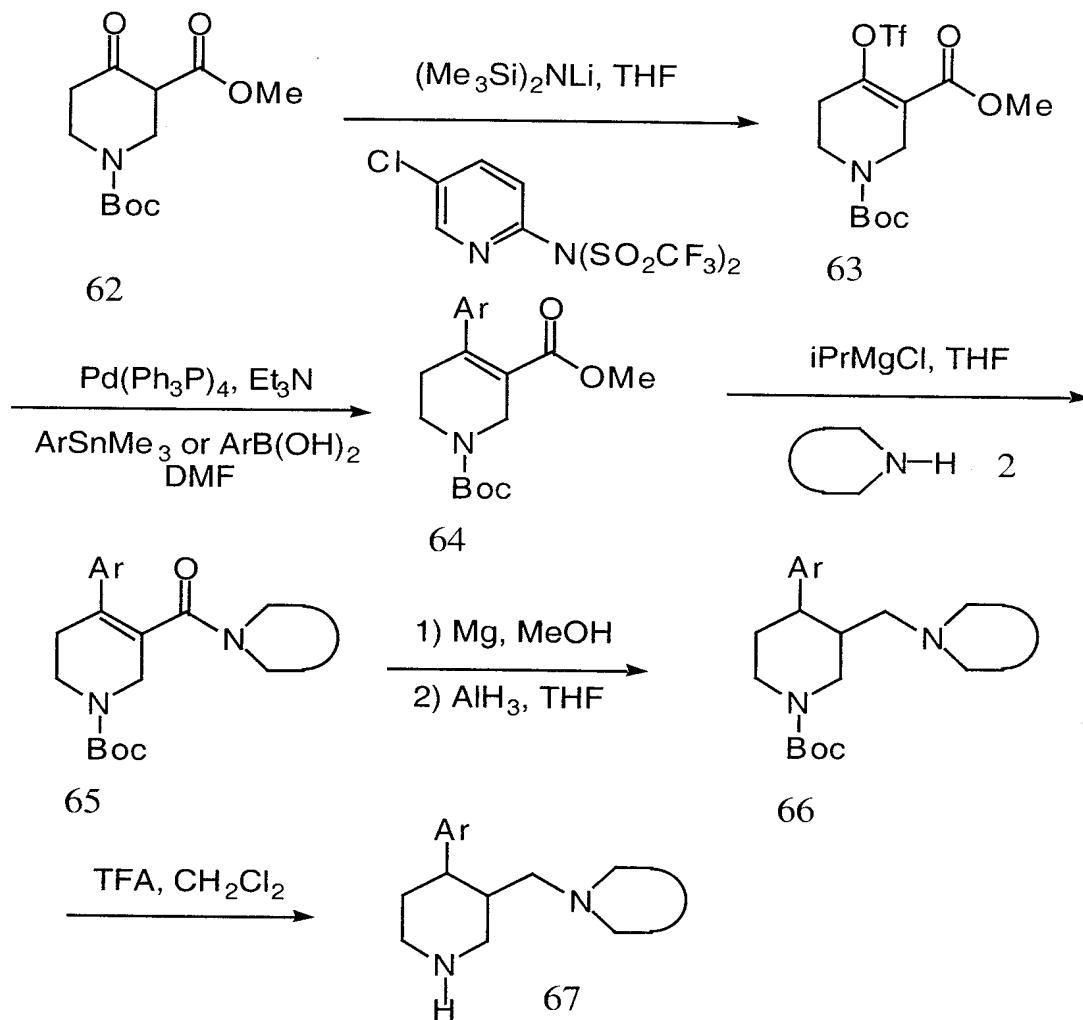
In Scheme 16, the preparation of 4-(3-phenyl-3-hydroxypropyl) piperidines is described. Oxidation of compound 44 under Swern conditions gives 5 aldehyde derivative 53. It is then reacted with diethyl(2-aryl-2-oxoethyl)phosphonate and a base such as KOtBu in a solvent such as THF to give the conjugated ketone derivative 54. Reduction with hydrogen in the presence of Pd/C preferentially at 50 psi gives the hydroxy compound 55 which is converted to piperidine derivative 56 as 10 previously described. Prior to deprotection, compound 55 can be further modified as depicted in Scheme 15.

SCHEME 17



The synthesis of a framework for piperidine-based chemokine receptor modulators is given in Scheme 17. Enolate formation of the 4-piperidone derivative 35 followed by formation of the vinyl triflate with either 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine or with N-phenyltriflimide provides compound 57. Palladium-catalysed carbonylation in the presence of methanol then affords unsaturated ester 58. Conjugate addition of an aryl magnesium halide reagent in the presence of a copper catalyst and chlorotrimethylsilane to this species, followed by treatment with the magnesium salt of a suitable cyclic amine, then yields amide 59. Reduction with LiAlH₄ or borane-THF affords the tertiary amine 60, which is hydrogenated under standard conditions to the secondary piperidine 61. This compound is alkylated, acylated or sulfonated by analogy to the conditions described for compound 21 in Scheme 4.

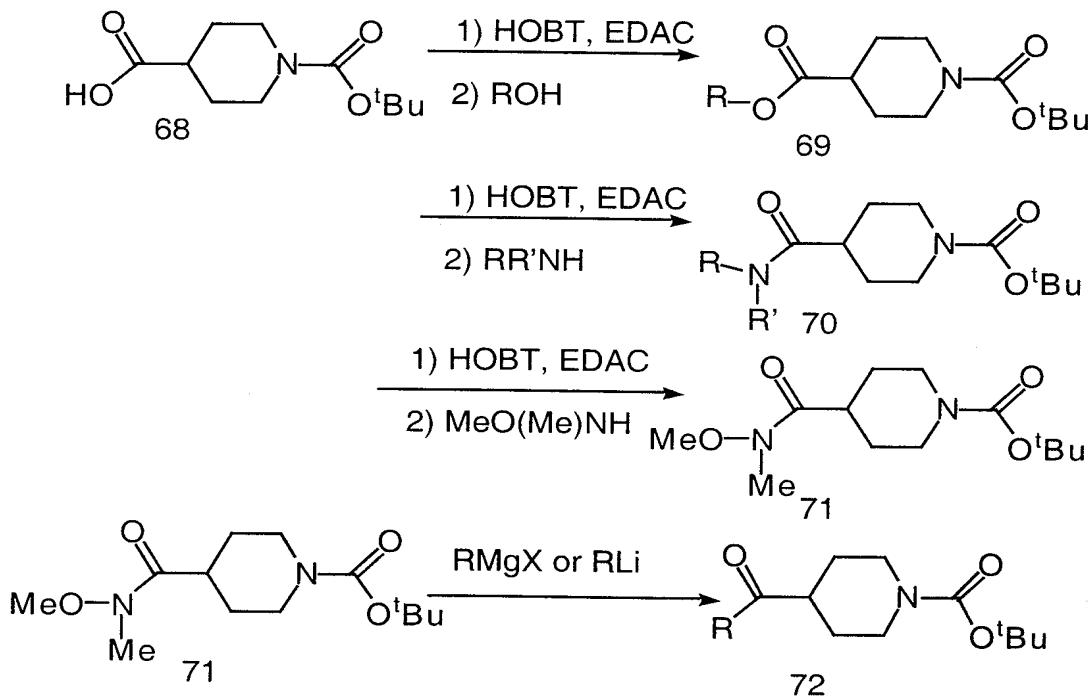
SCHEME 18



Synthesis of a piperidine derivative with an alternate presentation of the 3- and 4-substituents is given in Scheme 18. Formation of the enolate of ketoester 5 (prepared from commercially available 3-carbomethoxy-4-oxopiperidine and Boc anhydride) followed by addition of either 2-[N,N-bis(trifluoro-methylsulfonyl)amino]-5-chloropyridine or N-phenyltriflimide provides vinyl triflate 63. Palladium-mediated coupling with a suitable aryl stannane or aryl boronic acid provides unsaturated ester 64. Treatment of this compound with the magnesium salt of a suitable cyclic amine 10 then affords amide 65, which can be reduced successively with magnesium metal in methanol followed by alane in THF, to provide the tertiary amine 66. Removal of the

Boc group under standard acidic conditions yields secondary amine 67, which can be alkylated, acylated or sulfonated by analogy to the conditions described in Scheme 6.

SCHEME 19



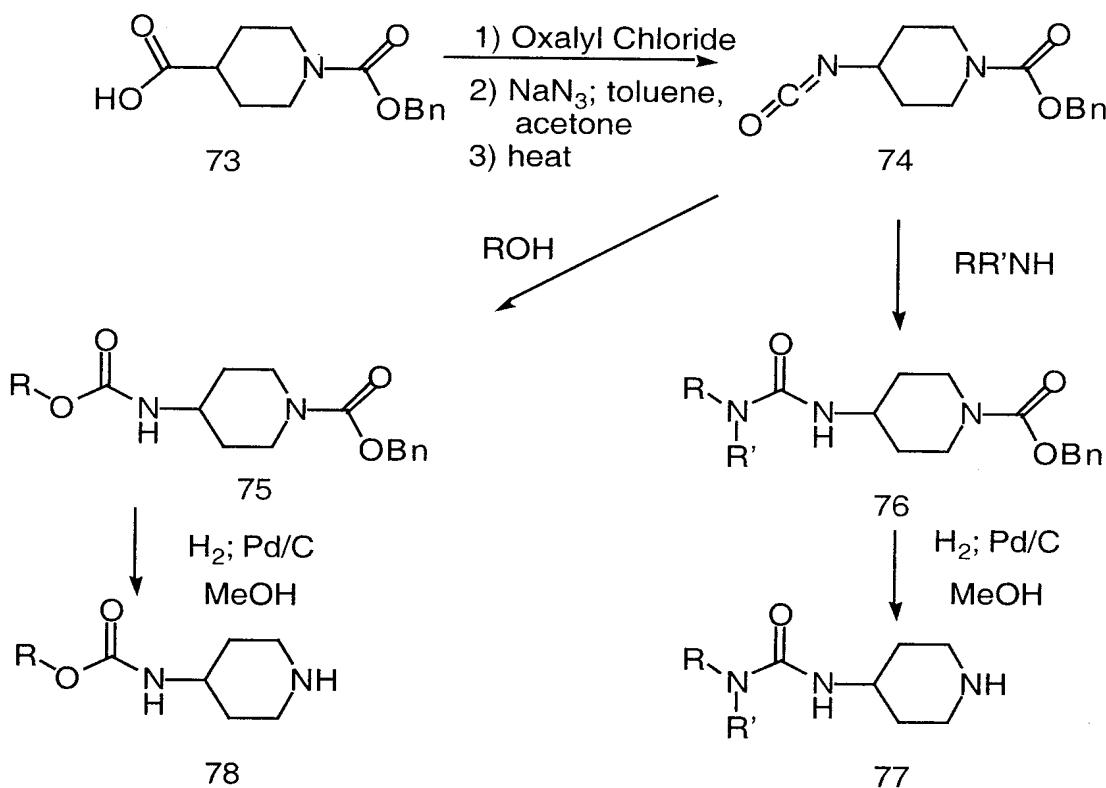
5

The cyclic amine II employed in the preceding Schemes can be obtained commercially in many cases or is prepared by a number of procedures. For example, as shown in Scheme 19, compound 68, the N-t-butoxycarbonyl protected form of isonipeptic acid (4-piperidine-carboxylic acid) is activated under standard conditions, for example with a carbodiimide, and converted into ester 69 or amide 70. Alternatively, acid 68 is converted into the N-methyl-N-methoxy amide, 71, which upon reaction with organomagnesium and organolithium reagents forms the ketone 72. The Boc group of 69, 70 and 72 is removed under acidic conditions to provide the corresponding secondary amines.

10

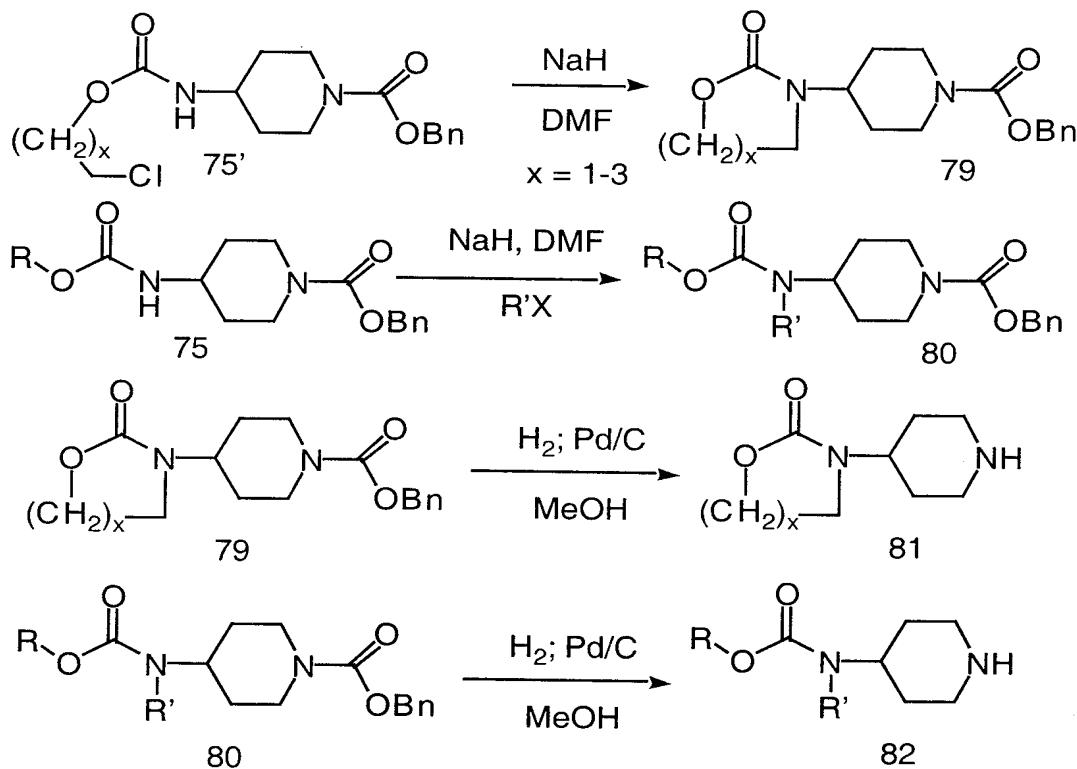
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SCHEME 20



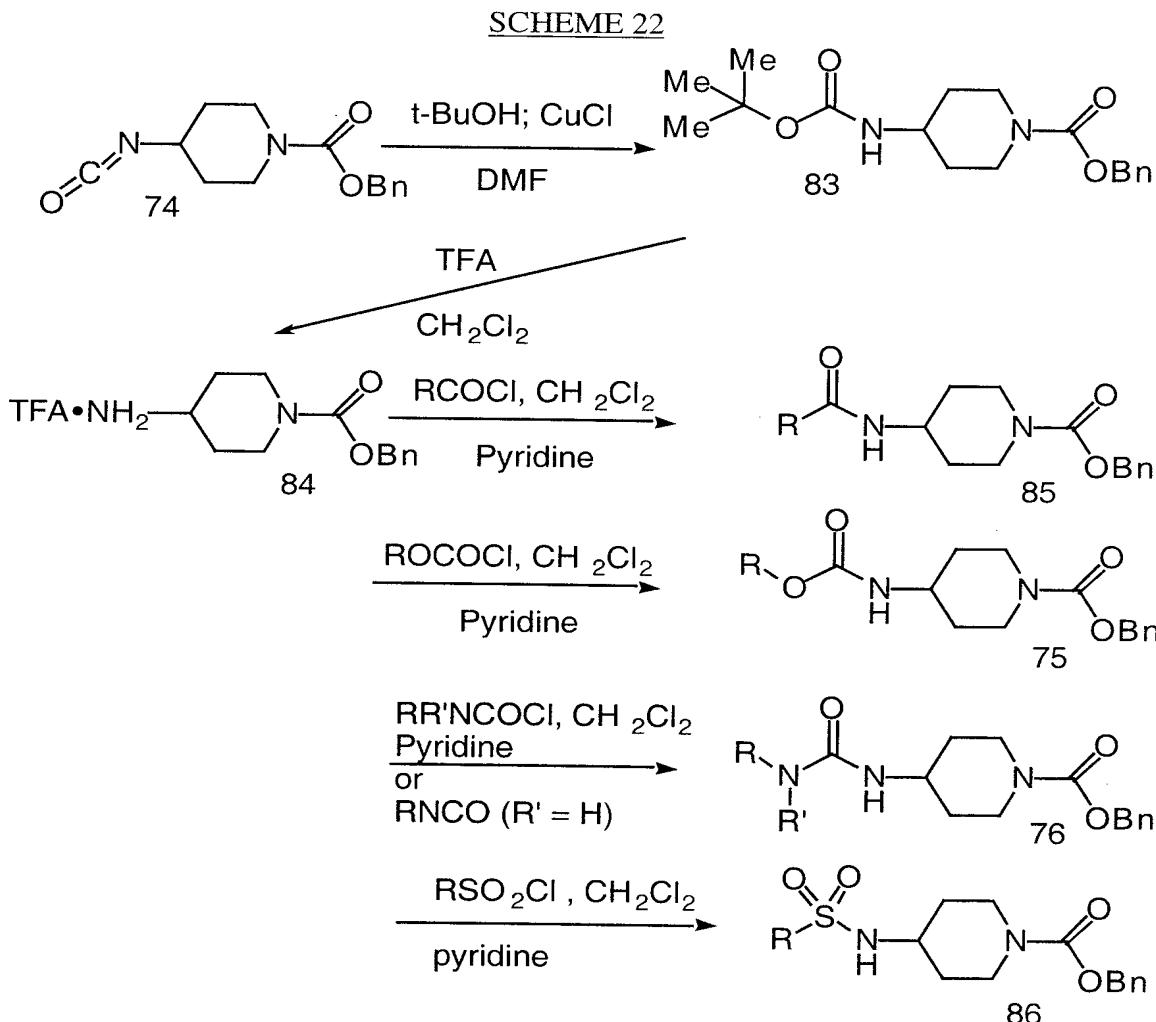
Alternatively, CBZ-protected piperidine 73 is allowed to react with oxalyl chloride and then sodium azide, to provide the corresponding acyl azide, which 5 can then be thermally rearranged to isocyanate 74 (Scheme 20). Compound 74 is treated with an alcohol ROH or an amine RR'NH to form carbamate 75 or urea 76, respectively, each of which is deprotected with hydrogen in the presence of palladium on carbon to secondary amines 77 or 78.

SCHEME 21



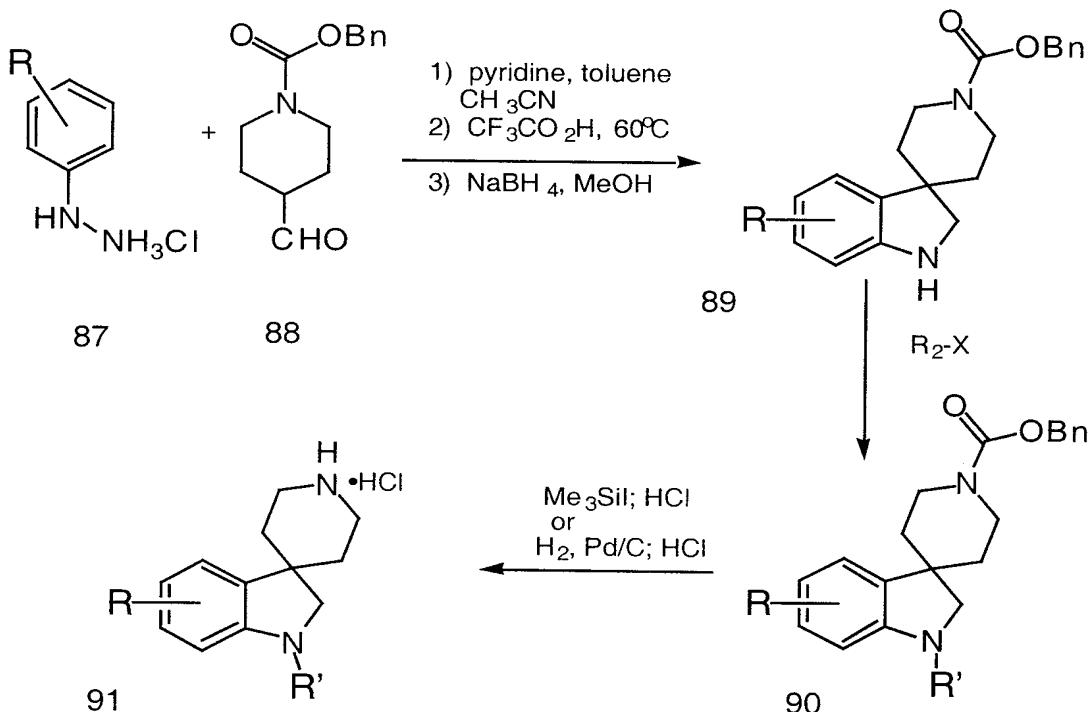
If the carbamate 75 has $\text{R} = -(\text{CH}_2)_x\text{CH}_2\text{Cl}$, where $x = 1-3$, then

treatment with a suitable base, such as sodium hydride, lithium hexamethyldisilazide
5 or potassium t-butoxide, can induce cyclization to compound 79 (Scheme 21). For
other R groups, carbamate 75 is treated with an alkylating agent R'X, where R' =
primary or secondary alkyl, allyl, propargyl or benzyl, while X = bromide, iodide,
tosylate, mesylate or trifluoromethanesulfonate, in the presence of a suitable base,
such as sodium hydride, lithium hexamethyldisilazide or potassium t-butoxide, to give
10 derivative 80; a similar process can be employed for urea 76. In each case, removal of
the CBZ protecting group under standard conditions provides the secondary amines
81 and 82.



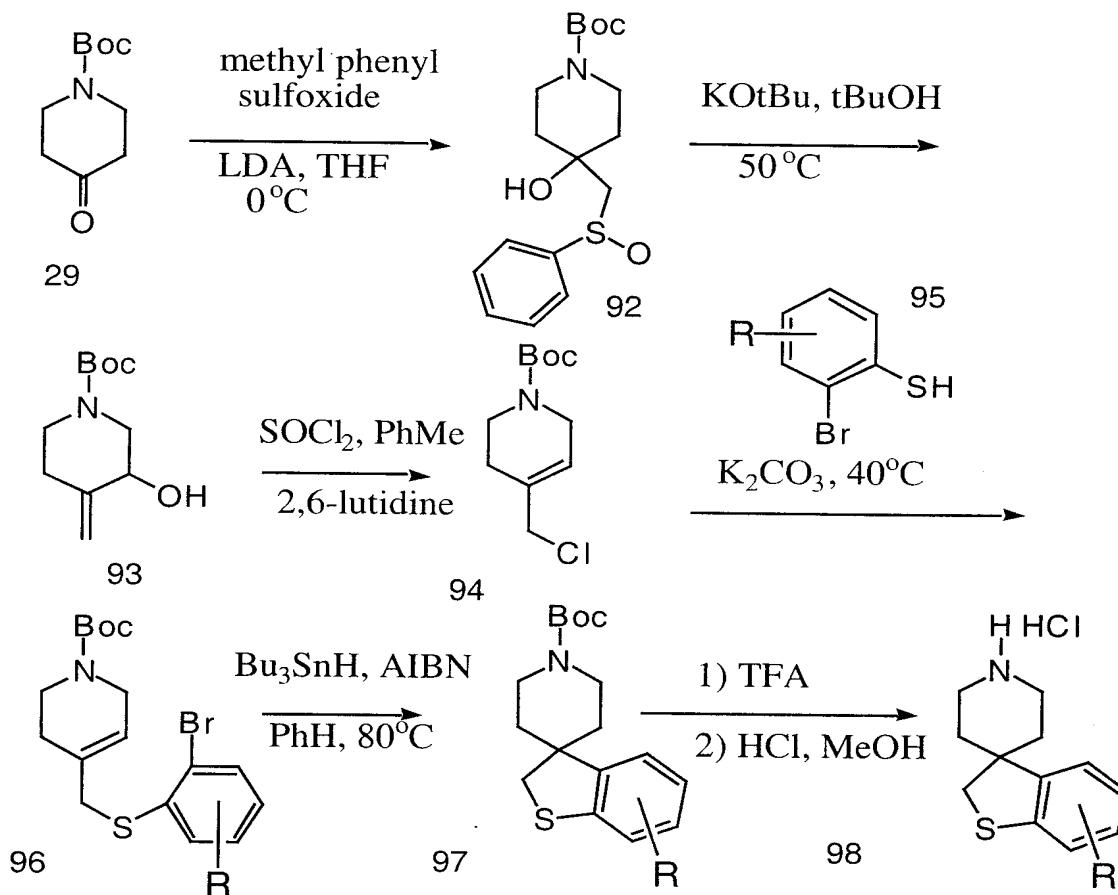
Additional derivatization of a piperidine with nitrogen functionality at C4 is carried out as shown in Scheme 22. For example, if the ring nitrogen is 5 protected with a CBZ group, as with isocyanate 74, treatment with tert-butyl alcohol in the presence of copper(I) chloride, provides Boc derivative 83. This compound is selectively deprotected to the free amine 84. This amine is acylated with an acid chloride, a chloroformate, an isocyanate, or a carbamyl chloride, to provide compounds 85, 75 or 76. Alternatively, amine 84 is sulfonated with an alkyl or 10 arylsulfonyl chloride, to give sulfonamide 86. Compounds 85 and 86 optionally is alkylated under the conditions given above. As shown in Scheme 21, removal of the CBZ group under reductive conditions gives the desired secondary amines.

SCHEME 23



Substituted spiro(indoline-3,4'-piperidine) derivatives can be prepared as shown in Scheme 23 starting from the substituted phenylhydrazine 87 and the 5 aldehyde 88. Following the Fischer indole reaction and reduction of the intermediate imine with a mild reducing agent such as sodium borohydride, the indoline 89 can be combined with an electrophile such as an acyl chloride or a sulfonyl chloride. The protecting group on compound 90, for example a benzyloxycarbonyl group, can be removed by treatment with hydrogen in the presence of palladium on carbon or by 10 exposure to trimethylsilyl iodide, to give the deprotected substituted spiro(indoline-3,4'-piperidine) 91.

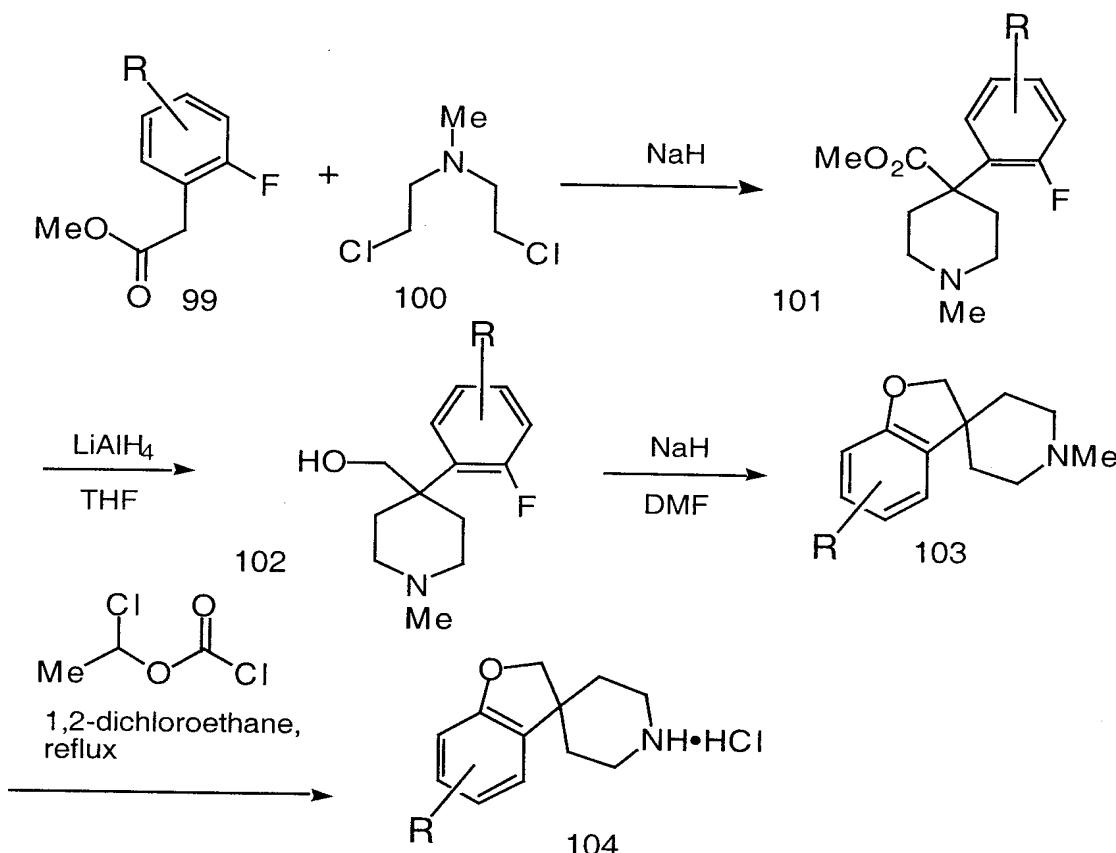
SCHEME 24



Preparation of spiro(2,3-dihydrobenzothiophene-3,4'-piperidine)

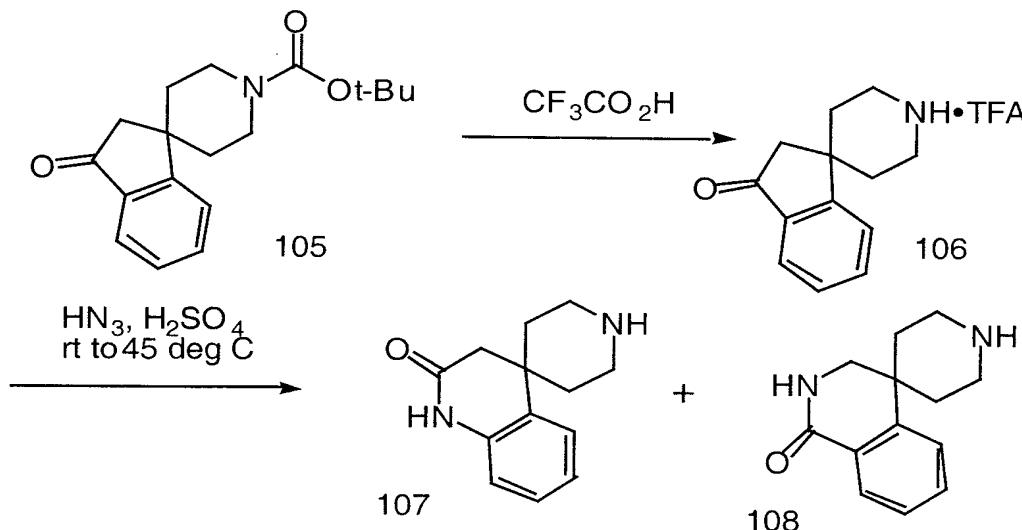
5 derivatives is shown in Scheme 24. Reaction piperidone 29 with the lithium salt of methyl phenyl sulfoxide affords adduct 92. Base-mediated elimination-rearrangement and basic cleavage provides the allylic alcohol 93. The alcohol is converted to rearranged allylic chloride 94 with thionyl chloride in toluene in the presence of 2,6-lutidine as a proton scavenger. Displacement of the chloride with the 2-
 10 bromothiophenol 95 provides allylic sulfide 96, which can be cyclized under radical conditions to give spiro(2,3-dihydrobenzothiophene-3,4'-piperidine) 97. Cleavage of the t-butoxycarbonyl group under standard conditions, such as trifluoroacetic acid, then provides the desired spirocycle 98.

SCHEME 25



5 Spiro(2,3-dihydrobenzofuran-3,4'-piperidine) derivatives are prepared
 as illustrated in Scheme 25. Treatment of an appropriately substituted ester of 2-
 fluorophenylacetate 99 with mechlorethamine hydrochloride 100 under basic
 conditions provides piperidine 101, which on treatment with a strong reducing agent
 such as lithium aluminum hydride produces the corresponding 4-(hydroxymethyl)
 compound 102. Cyclization with base provides benzofuran 103, and cleavage of the
 10 N-methyl group is then carried out using 1-chloroethyl chloroformate or other suitable
 N-demethylating agents, to provide the desired intermediate 104.

SCHEME 26



5 Spiro(2-oxo-1,2,3,4-tetrahydroquinoline-4,4'-piperidine) and spiro(1-
 10 oxo-1,2,3,4-tetrahydroisoquinoline-4,4'-piperidine) are prepared as shown in Scheme
 15 26. Starting from the spiro(2-oxoindane-3,4'-piperidine) LXXXVIII (described in
 Claremon, D.A. *et al*, European Patent 0 431 943 943 A2, Evans, B.E. *et al*, U.S.
 Patent 5,091,387, Davis, L. *et al*, U.S. Patent 4,420,485, all of which are incorporated
 by reference, and Parham *et al*, Journal of Organic Chemistry, **41**, 2628 (1976)),
 deprotection of the piperidine nitrogen is carried out by treatment with acid, for
 example trifluoroacetic acid, to provide ketone 106. After protection as the
 trifluoroacetamide, the product is exposed to hydrazoic acid in the presence of sulfuric
 acid. Heating of this mixture effects a Schmidt rearrangement, to provide both
 tetrahydroquinoline 107 and the tetrahydroisoquinoline 108. These spiro compounds
 are then separated and coupled to functionalized aldehydes by the methodology given
 above.

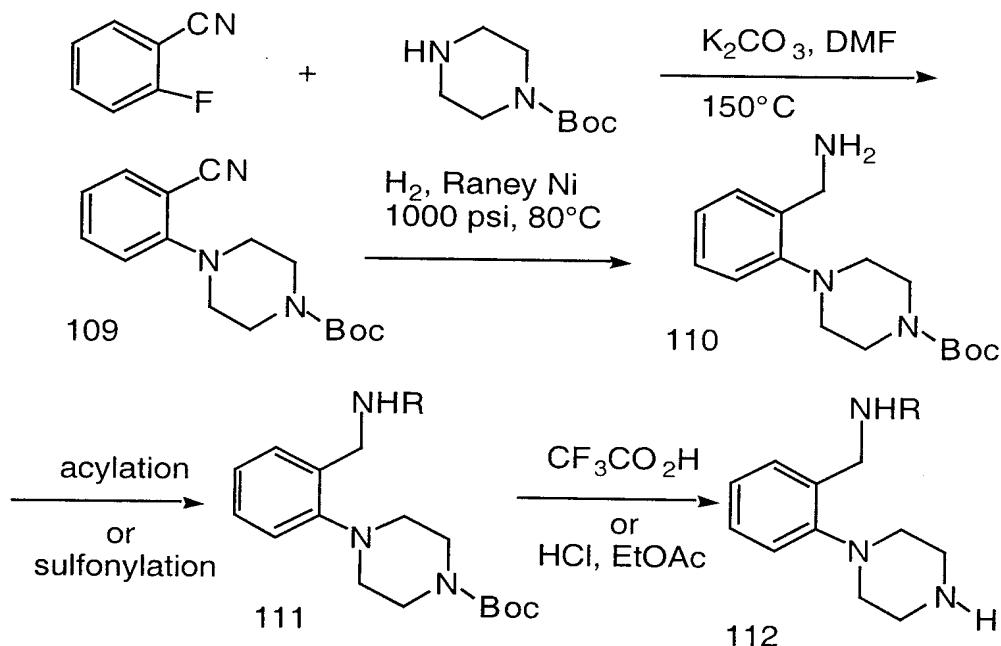
20 Cyclic amines (compound 2) which are 4-arylpiperazines functionality
 are prepared using methods described in the following Schemes. Starting materials
 are made from known procedures or as illustrated. Substituted purines are prepared as
 disclosed in US 5,057,517; imidazo(1,2-a)pyrazinyl, as disclosed in US 4,242,344;
 (1,2,4)-triazolo(1,5-a)pyrazinyl as disclosed in *J. Org. Chem.*, **1974**, **39**, 2143 and
J.C.S. Perkin I, **1980**, **506**; 1,7-naphthyridinyl as disclosed in *J. Org. Chem.*, **1963**, **28**,
 1753; furo(3,2-c)pyridinyl as disclosed in *J. Heterocyclic Chem.*, **1982**, **19**, 1207; and

substituted 6-H-7,8-dihydro-thiopyrano(3,2-d)pyrimidyl as disclosed in *Arch. Int. Pharmacodyn.* **1986**, 280, pp302-313.

5 Optionally, Compound III formed in the alkylation step is further modified in subsequent reactions. In one illustration of such an approach, the piperazine fragment may contain a nitro group, which is reduced to the amine after the coupling step. The resulting amine is further modified by acylation to provide the desired compounds. The piperazine fragment may also contain a protecting group such as a benzyl ester or a t-butyl ester. After reductive amination the protecting group is removed and the resulting acid is further reacted to provide additional 10 analogs. Alternatively, the aldehyde portion may also contain a protecting group such as a t-butoxycarbonyl for an amino function. After reductive amination, the t-butoxycarbonyl group is removed by treatment with a strong acid such as trifluoroacetic acid, formic acid or hydrochloric acid and the resulting amine may be acylated to provide other analogs.

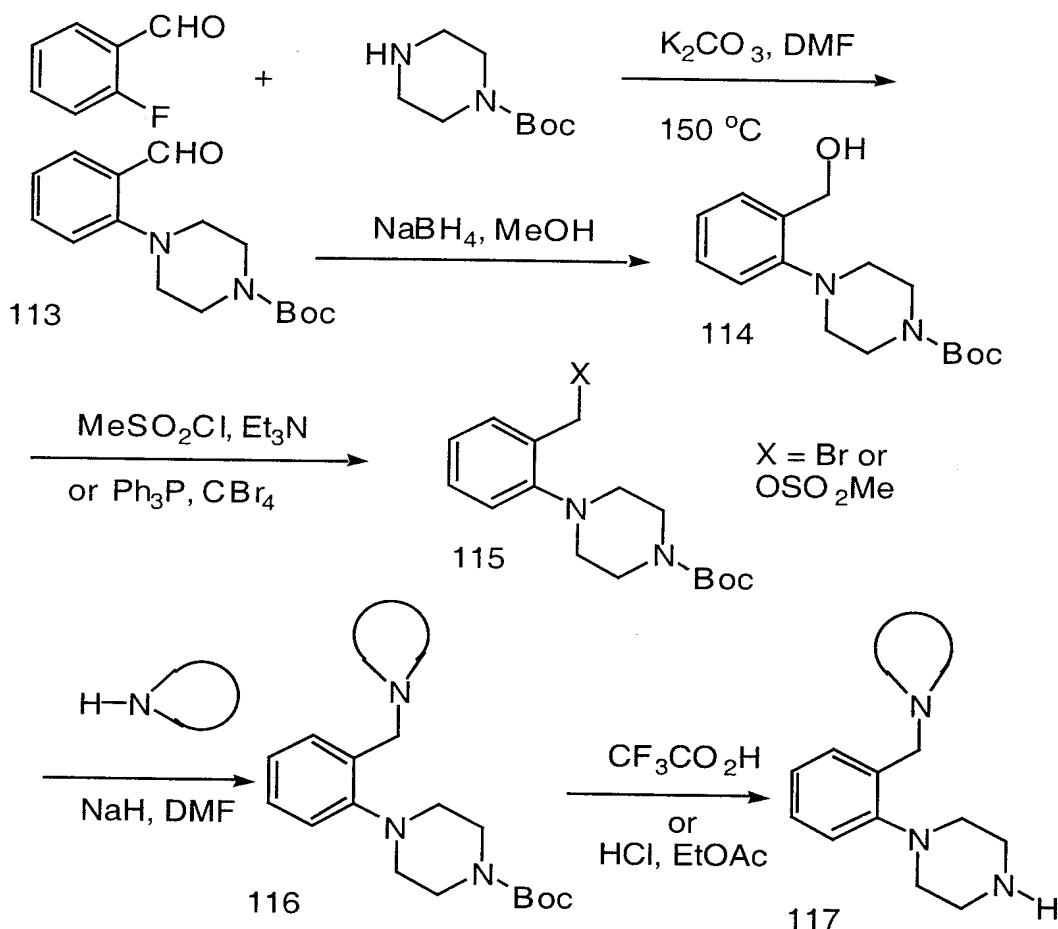
15 The piperazine starting materials used in the coupling reaction are prepared using methods described in the literature; more specifically as described in US Patent No. 5,057,517; US Patent No. 4,242,344; *J. Org. Chem.*, **1974**, 39, 2143 and *J.C.S. Perkin I*, **1980**, 506; *J. Org. Chem.* **1963**, 28, 1753; *J. Heterocyclic Chem.*, **1982**, 19, 1207; *Arch. Int. Pharmacodyn.* **1986**, 280, pp302-313 ; Meurer, L.. C. *et al.*, *J. Med. Chem.*, **1992**, 35, 3845-3857. None of these published compounds are 20 disclosed to be chemokine receptor modulators. Alternatively, the piperazine substrates is prepared as illustrated in Schemes 27-30.

SCHEME 27



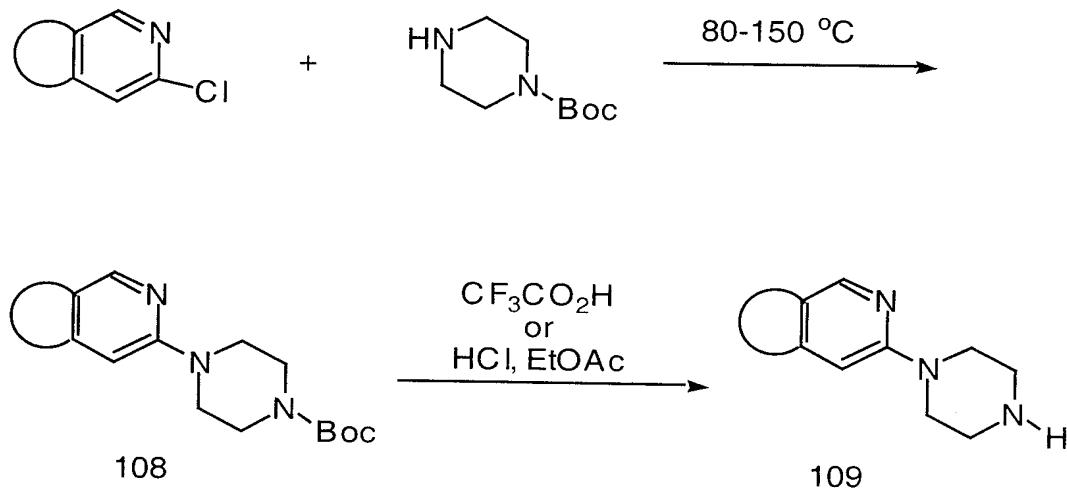
Substituted 4-arylpiperazines are prepared from appropriate fluorobenzene derivative as shown in Scheme 27. Thus, reaction of 2-fluorobenzonitrile with 1-t-butoxycarbonylpiperazine in the presence of a base such as K_2CO_3 gives 1-t-butoxycarbonyl-4-(2-cyanophenyl)-piperazine (compound 109). Reduction of the cyano group by hydrogenation in the presence of Raney nickel or by other known methods gives benzyl amine 110, which is acylated or sulfonylated, to provide piperazine 111. The t-butoxycarbonyl protecting group is removed under acidic conditions, for example by treatment with trifluoroacetic acid or anhydrous HCl to give 1-unsubstituted piperazine 112 which can be used in the reductive amination or alkylation steps described in Scheme 1. Similar reactions using 2-chloro-nitrobenzene in the place of 2-fluorobenzonitrile provides compounds containing a substituted aniline. Analogs containing a benzoic acid or its derivatives are prepared by substituting 2-fluorobenzoic acid in this sequence.

SCHEME 28



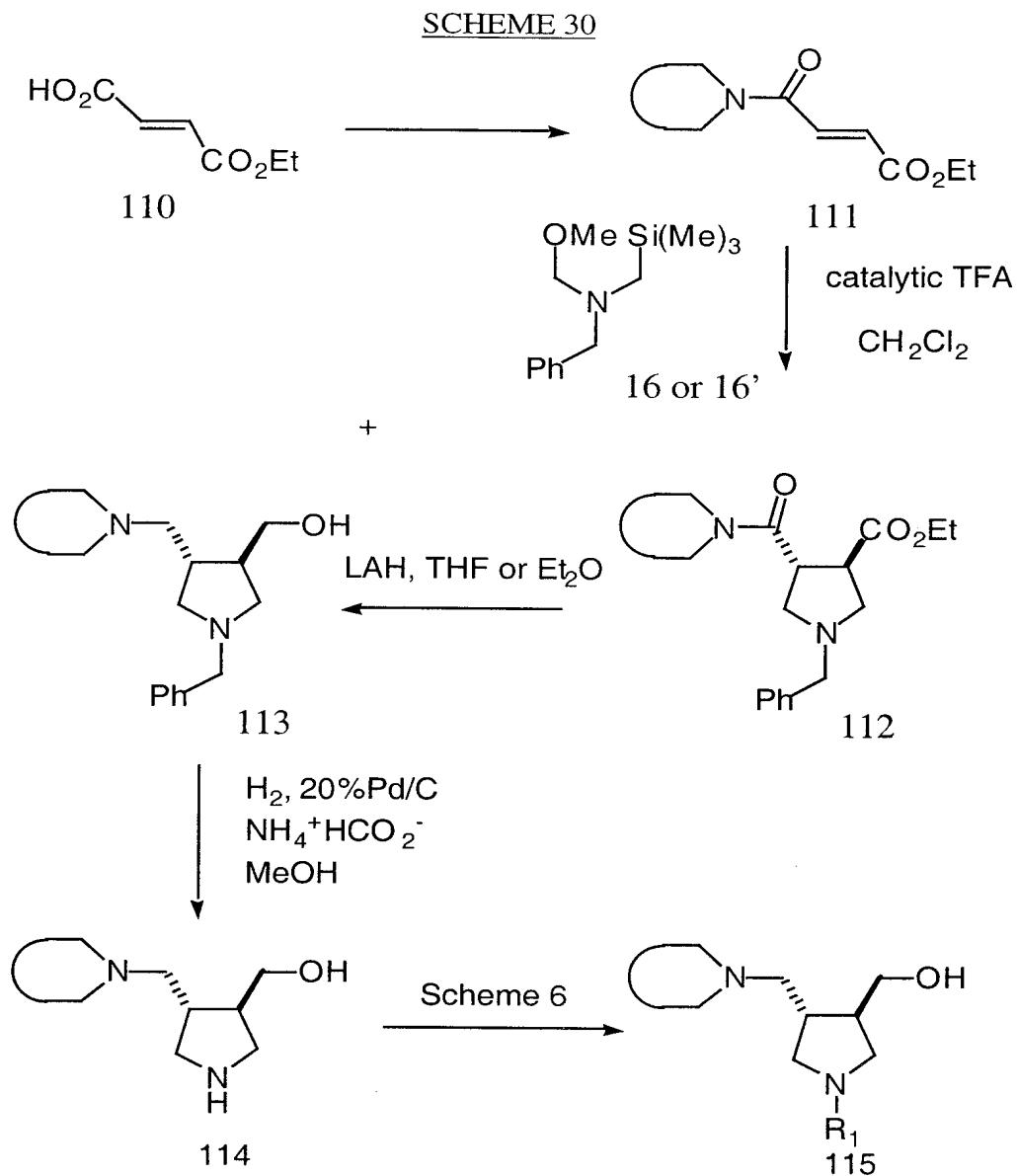
Arylpiperazine derivatives containing heterocyclic substituents are synthesized as shown in Scheme 28. Reaction between 2-fluorobenzaldehyde and 1-t-butoxycarbonylpiperazine gives 1-t-butoxycarbonyl-4-(2-formylphenyl)-piperazine compound 113. Reduction of this aldehyde and treatment of the alcohol 114 with methanesulfonyl chloride gives 115 (X = mesylate), while treatment of 114 with triphenylphosphine and carbon tetrabromide gives 115 (X = bromide). Displacement of the leaving group by a heterocycle such as imidazole in the presence of a base provides piperazine 116. Removal of the t-butoxycarbonyl protecting group under standard anhydrous acidic conditions furnishes compound 117 which is used in the coupling reactions described in Scheme I.

SCHEME 29



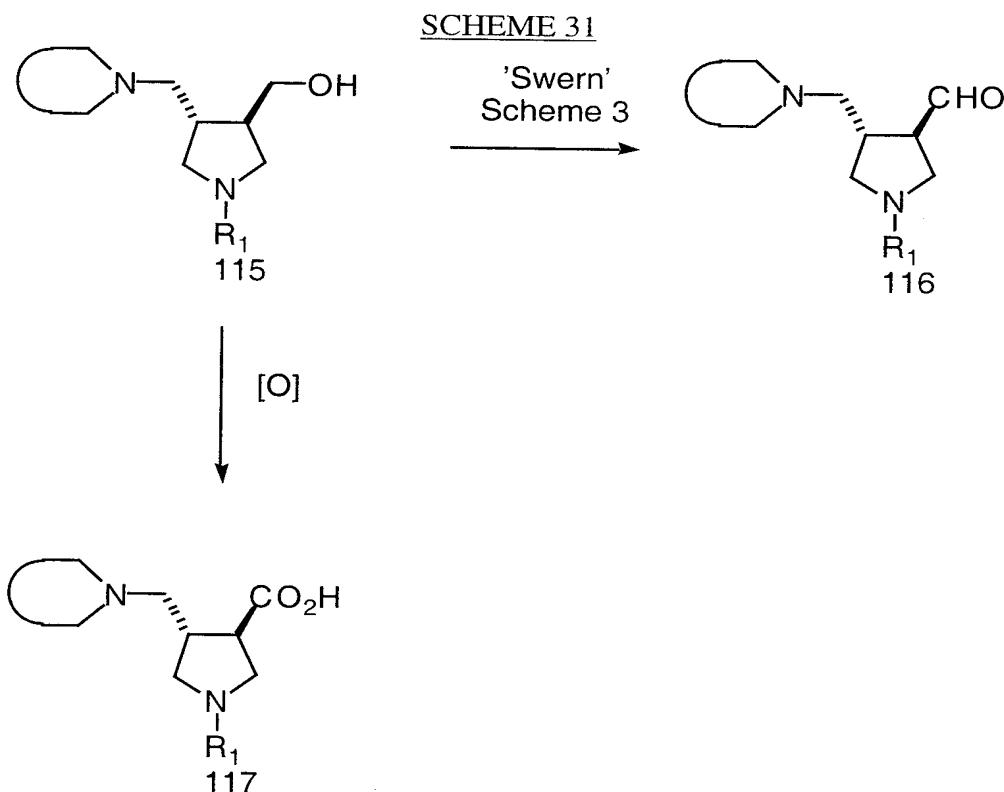
Preparation of piperazines containing a heteroaryl substituent is outlined in Scheme 29. Reaction of 1-t-butoxycarbonyl-piperazine with a chloro substituted heteroaromatic compound such as 8-chloro-1,7-naphthyridine or 8-chloro-(1,2,4)-triazolo(1,5-a)pyrazine gives N-protected piperazine 108. Removal of the t-butoxycarbonyl protecting group under standard conditions by treatment with acid provides piperazine 109 for use in the coupling steps outlined in Scheme 1.

10

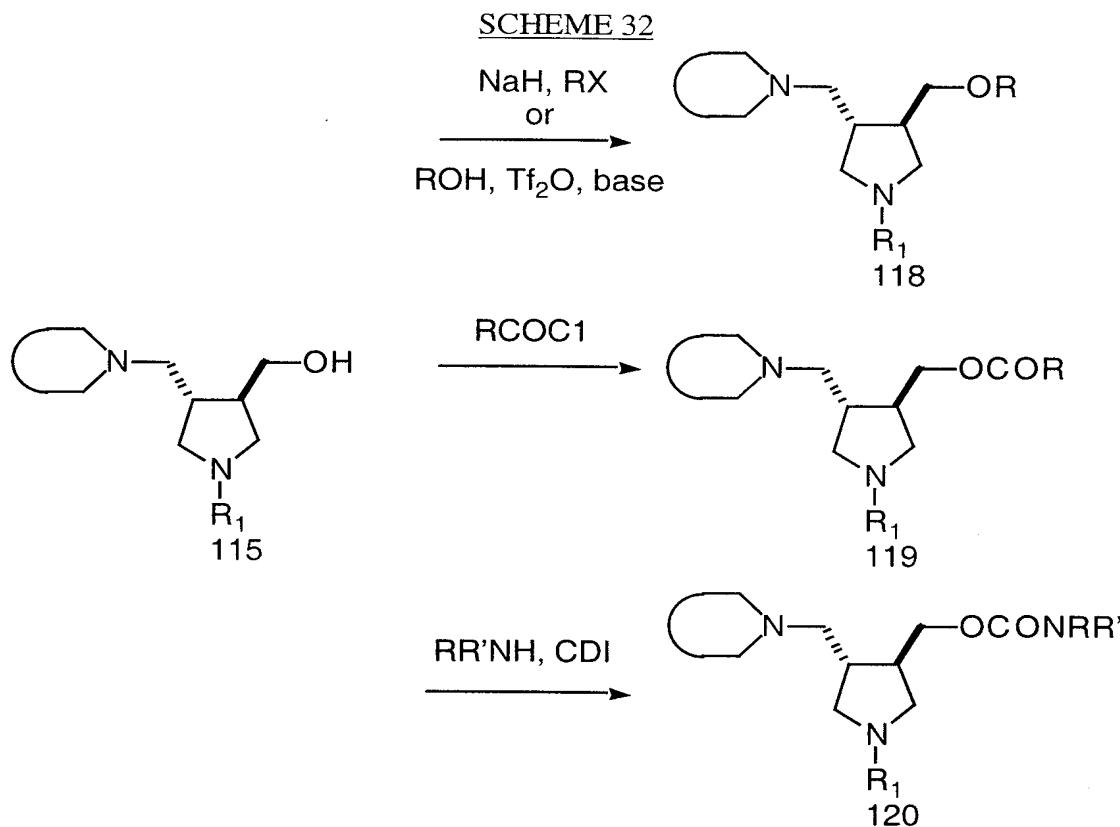


A variation of Reaction Schemes 1 to 9 is described in Reaction Scheme 30. Monoethylsuccinate 110 is coupled with cyclic amine 2 as described in Reaction Scheme 1 to give amide 111. Amide 111 is cyclized with N-benzyl-N-methoxymethyl-N-(trimethylsilyl)-methylamine (16) or N-allyl-N-methoxymethyl-N-(trimethylsilyl)-methylamine (16') as described in Reaction Schemes 3 or 5 to give pyrrolidine derivative 112. Reduction of compound 112 with LAH in THF or ether gives primary alcohol 113. The protecting group on the nitrogen of compound 113 can be removed as described in Reaction Scheme 3 to give compound 114. In the

case where the protecting group is allyl, it is removed as described in Reaction Scheme 5. The nitrogen position of compound 114 can be functionalized as described in Reaction Scheme 6, when the conditions are compatible with the primary alcohol. For example, compound 114 is reacted with an acid chloride in a solvent such as 5 methylene chloride. To the reaction mixture is then added methanol or ethanol with added stirring to remove any unintended acylation of the primary alcohol.



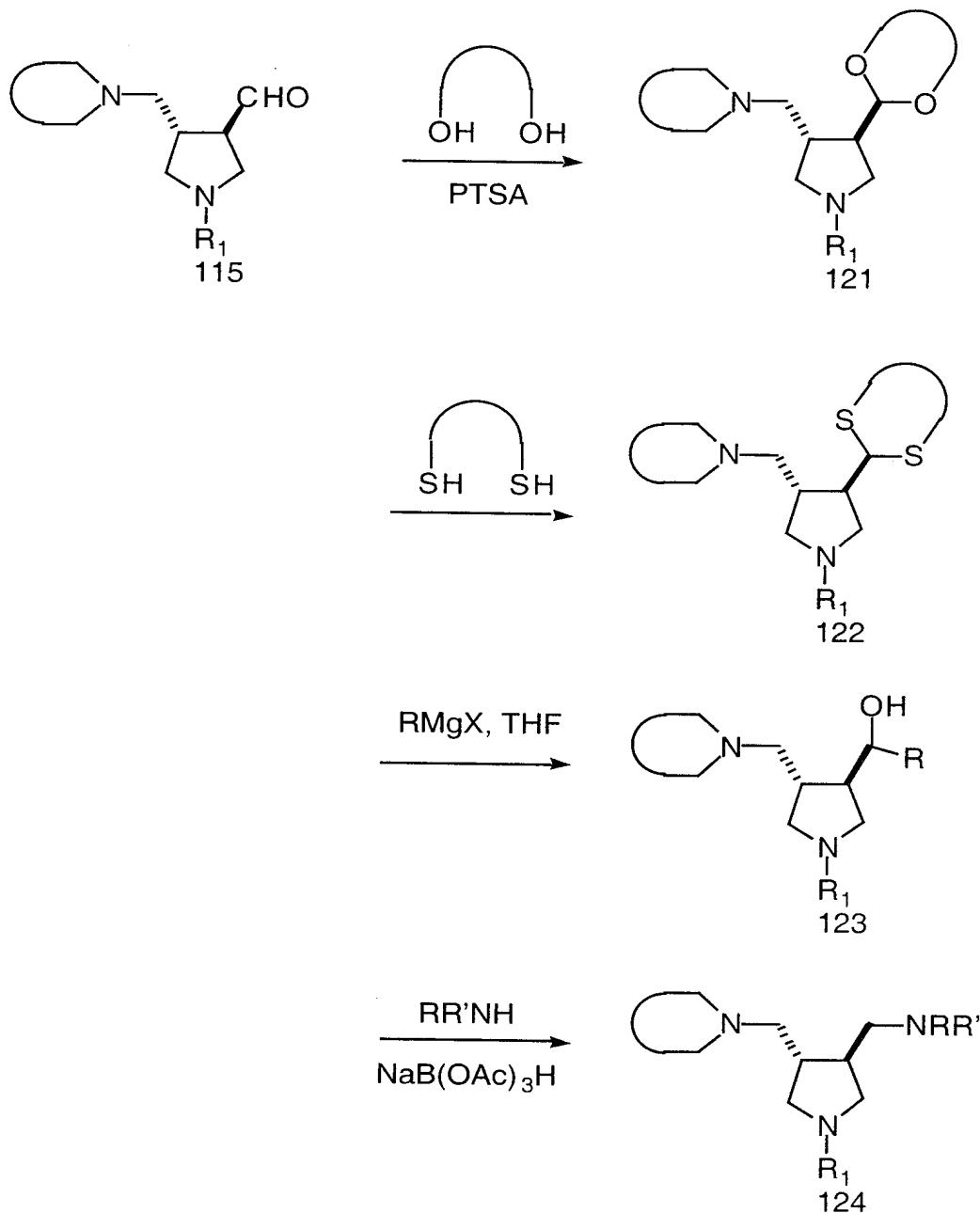
10 In Reaction Scheme 31, compound 31 is oxidized to aldehyde derivative 116 utilizing Swern-type conditions described in Scheme 3. Compound 115 can also be oxidized to acid derivative 117 utilizing various chromium trioxide-based reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1167-1171 (1992)).



Primary alcohol 115 may be further modified in numerous ways including conversion to ether 118, ester 119 and carbamate 120 as described in

5 Reaction scheme 15. Alternatively, aryl ethers are prepared using triaryl bismuthine reagents (Sinclair et. al., *Bioorg. Med. Chem. Letters* 1995, 5, 1035 and references cited therein). Further modifications can be achieved utilizing standard methodologies.

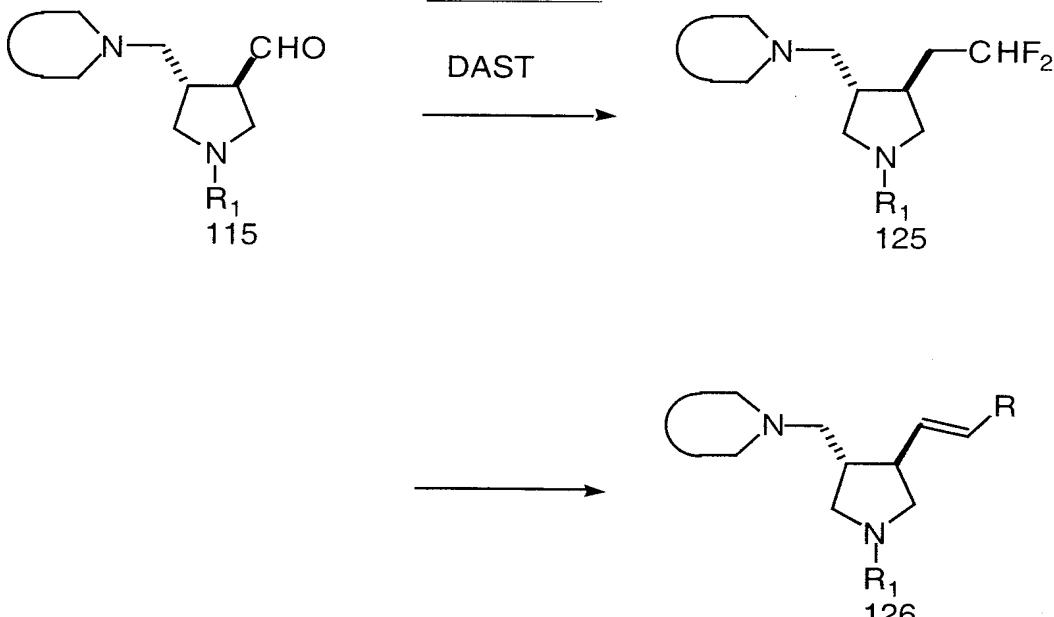
SCHEME 33



Aldehyde 115 can be converted to acetals as demonstrated in Scheme 33. Heating a solution of 115 with a diol such as ethylene glycol and an acid such as 5 paratoluenesulfonic acid in a solvent such as benzene or toluene gives 1,3-dioxolane derivative 121. Other diols give corresponding acetals. Thioacetal derivatives (122) may be prepared by similar means. Aldehyde 115 may be reacted with nucleophiles

such as Grignard reagents to give secondary alcohol derivatives 123. Aldehyde 115 can also be converted to amine 124 as described in Rxn Scheme 1.

SCHEME 34



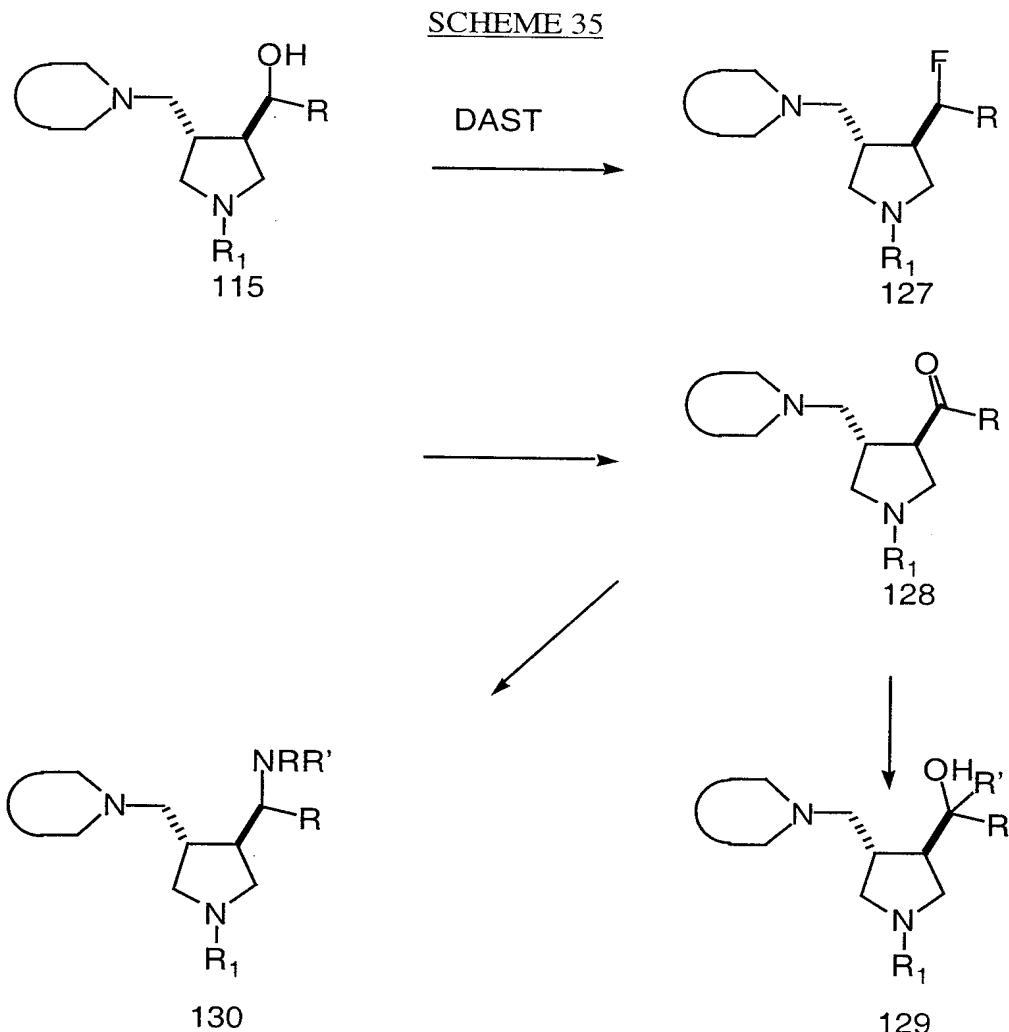
5

In Scheme 34, aldehyde 115 can be converted to the difluoro derivative 125 using SF₄ or the commercially available DAST (Et₂NSF₃) (see March J.

"Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 908 -

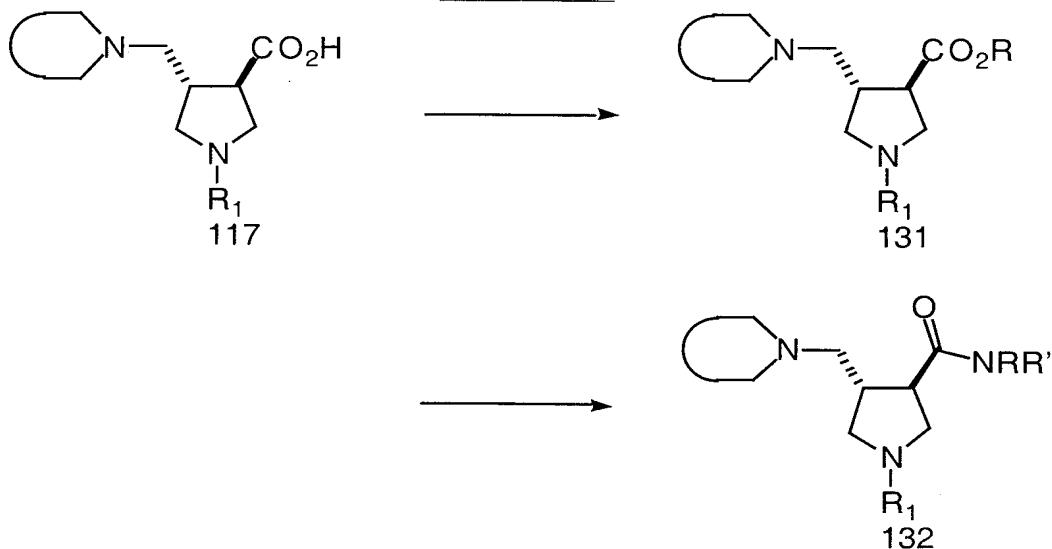
910 (1992)). Aldehyde 115 can be converted to olefin derivatives (126) by a variety

10 of standard olefination conditions including Wittig, Horner-Emmons-Wadsworth and related reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 956-963 (1992)).



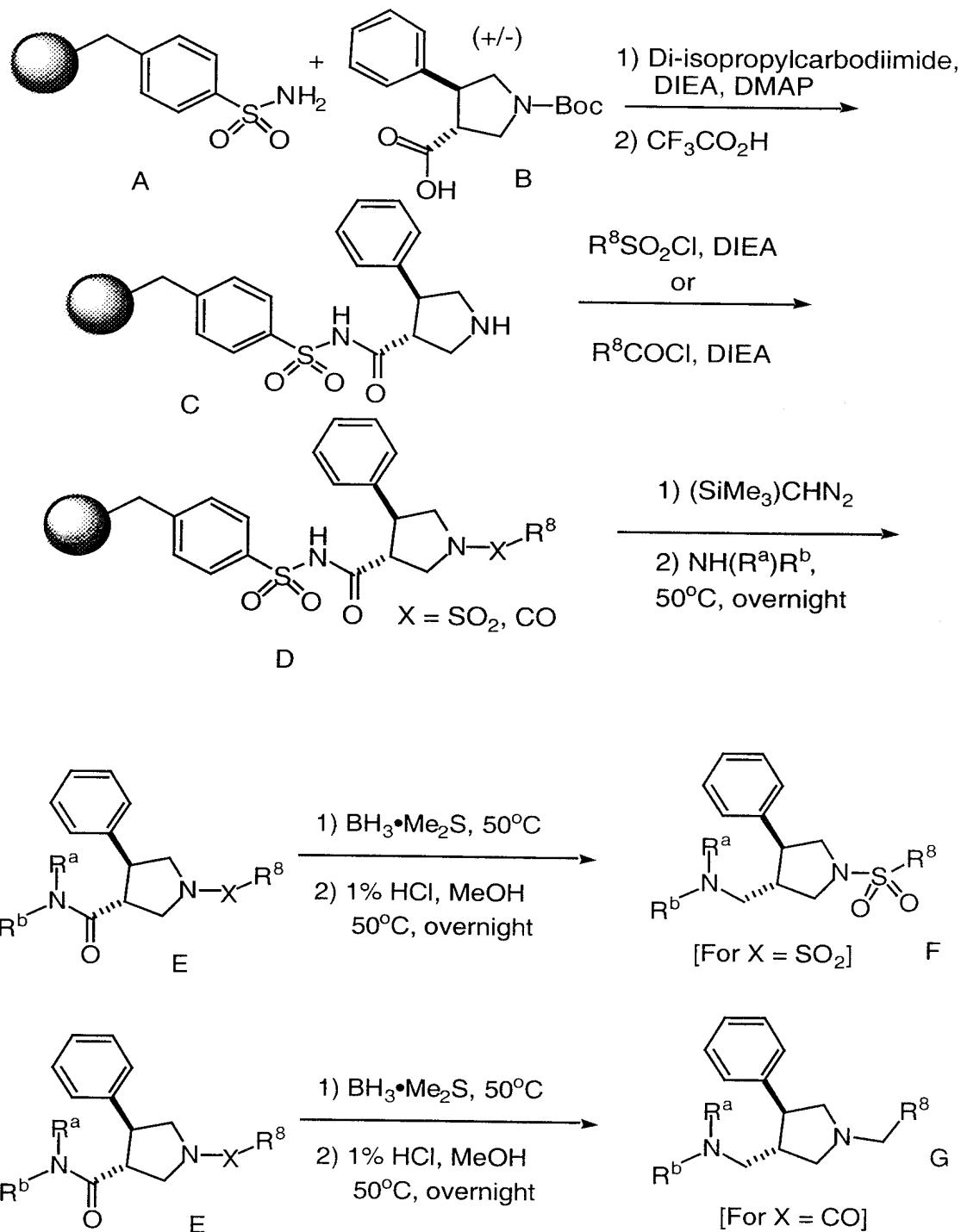
Secondary alcohol 115 can be converted to ether, ester and carbamate derivatives as described in Scheme 32. It may also be converted to the fluoro derivative 127 using DAST as described in Reaction Scheme 34 and by March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 432 (1992)). It may also be oxidized to ketone 128 with various chromium trioxide-based reagents (see March J. "Advanced Organic Chemistry", 4th ed., John Wiley & Sons, New York, pp. 1167-1171 (1992)). Ketone 128 can be converted to tertiary alcohol 129 by using nucleophiles such as Grignard reagents. Ketone 128 can also be converted to amine 130 as described in Reaction Scheme 1.

SCHEME 36



In Scheme 36, acid derivative 117 can be converted to ester derivative 131 using standard conditions such as reaction with an alcohol with an acid such as 5 TFA or HCl. Alternatively, acid 117 may be activated as an acid chloride using thionyl chloride or oxalyl chloride followed by reaction with an alcohol. Methyl esters can be prepared with diazomethane. Activation of acid 117 with a reagent such as BOP-Cl [bis(2-oxo-3-oxazolidinyl)phosphinic chloride] and a base such as Et₃N in methylene chloride followed by addition of an alcohol or amine gives ester 131 or 10 amide derivative 132. A variety of other standard amide coupling conditions may also be utilized.

SCHEME 37



Preparation of target pyrrolidines using solid support technology is outlined in Scheme 22. Coupling of intermediate B to a commercially available 4-sulfamylbenzoyl polystyrene resin A (or a alkyl sulfamyl resin) is carried out with diisopropylcarbodiimide or with other activating agents, for example

5 dicyclohexylcarbodiimide, EDAC, oxalyl chloride, etc. Agents that result in the formation of the symmetrical anhydride from B (which then serves as the acylating agent) are also suitable for this purpose. Removal of the Boc group is carried out with trifluoroacetic acid or other acidic reagents, to give resin-bound pyrrolidine C. This intermediate is then coupled with sulfonyl chlorides or carbonyl chlorides in the

10 presence of a suitable amine, preferably a hindered tertiary amine such as diisopropylethylamine (DIEA), lutidine, DBU, etc., to provide the N-functionalized pyrrolidine D. Alkylation of the acyl sulfonamide nitrogen can be carried out with trimethylsilyldiazomethane, diazomethane, with bromoacetonitrile in the presence of DBU and DMF, or under Mitsunobu conditions with a phenol such as

15 pentafluorophenol. Reaction of the resulting N-alkylated intermediate with an amine $\text{NH}(\text{Ra})\text{Rb}$ at a temperature between 0 and 140°C , preferably around 50°C , for 4-24 hr, preferably about 14 hr, then cleaves the pyrrolidine from the resin as amide E. Reduction of the newly formed amide (and other amide functionality, if present) with borane methyl sulfide complex (or other hydride reducing agents, such as borane-

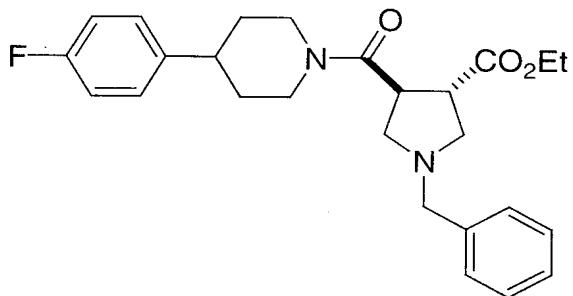
20 pyridine, borane-THF, lithium aluminum hydride, lithium di-(sec)butyl borohydride, etc) followed by hydrolysis with dilute hydrogen chloride in methanol at a temperature between 0 and 140°C , preferably around 50°C , for 4-24 hr, preferably about 14 hr, provides either sulfonamide F or amine G.

25 Cyclic amines (compound II) from Scheme 1 which are spirocyclic piperidines are prepared using azacyclic starting materials prepared using methods described in the literature; more specifically, as described in Claremon, D.A. *et al*, European Patent Publication 0 431 943, Evans, B.E. *et al*, U.S. Patent 5,091,387, Davis, L. *et al*, U.S. Patent 4,420,485, and Parham *et al*, Journal of Organic Chemistry, 41, 2628 (1976). None of the compounds in the foregoing references are

30 alleged to be chemokine receptor modulators.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1



1-Benzyl-3-(RS)-[4-(4-fluorophenyl)piperidinyl]carbonyl-4-(RS)-(ethoxy carbonyl)pyrrolidine

5

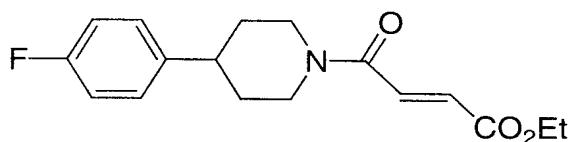
Step 1. 4-(4-Fluorophenyl)piperidine

A mixture of 10 g (47 mmol) of 4-(4-fluorophenyl) tetrahydro pyridine hydrochloride (Aldrich-Saylor) and 1.18 g of 10% Pd/C in 100 mL of degassed MeOH (N₂) was stirred under hydrogen at 45 psi for 18 h. The reaction mixture was

10 then filtered though a thin pad of celite eluting with MeOH. The filtrate was concentrated and the residue was stirred in 75 mL of ether. To it at 0 °C was added 5 g of solid NaOH. The layers were separated and the aqueous layer was extracted with ether. The combined organic fractions were washed with sat'd NaCl solution, dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was crystallized

15 from cold heptane to give 10 g of the title compound.

Step 2. Ethyl-4-(4-(4-fluorophenyl)piperidinyl)fumarate



A solution of 2.87 g (20 mmol) of mono-ethylfumarate (Aldrich), 3.24 20 g (20 mmol of 4-(4-fluorophenyl)piperidine, 2.93 g (24 mmol) of 4-dimethylaminopyridine, and 7.67 g (40 mmol) of 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride in 40 mL of CH₂Cl₂ at rt was stirred for 2.5 h. The reaction mixture was diluted with CH₂Cl₂, washed with NaHCO₃, dried over Na₂SO₄, filtered. The filtrate was concentrated and the residue was purified by

chromatography (silica, acetone: hexanes, 1:3) to give 4.4 g of the title compound. ^1H NMR (CDCl_3) δ 7.44 (d, 1H, J = 15.5 Hz), 7.14 - 7.16 (m, 2H), 7.00 (t, 2H, J = 8.5 Hz), 6.77 (d, 1H, J = 15.5 Hz), 4.26 (q, 2H, J = 7 Hz), 1.33 (t, 3H, J = 7 Hz).

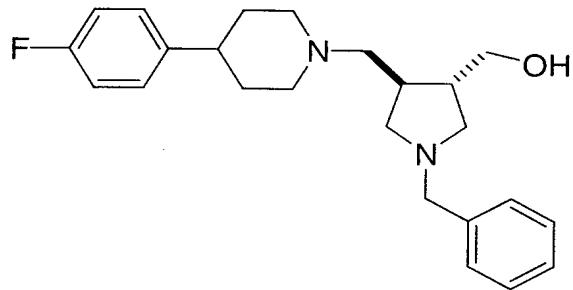
5 Step 2. 1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(RS)-(ethoxycarbonyl)pyrrolidine

To a solution of 4.4 g (14.4 mmol) of ethyl-4-(4-(4-fluorophenyl)piperidinyl)fumarate, and 4.1 g (17.3 mmol) of N-(methoxymethyl)-N-trimethylsilylmethylbenzylamine in 30 mL of CH_2Cl_2 at 0 °C was added 0.55 mL (7.2 mmol) of trifluoroacetic acid and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat'd NaHCO_3 . The combined organic fraction was dried over Na_2SO_4 , filtered and the filtrate was concentrated.

10 The residue was purified by chromatography (silica, acetone: hexanes, 1: 3) to give 6.4 g of the title compound. ^1H NMR (CDCl_3) δ 7.32 - 7.33 (m, 4H), 7.24 - 7.28 (m, 1H), 7.12- 7.16 (m, 2H), 7.00 (t, 2H, J = 8.2 Hz), 4.81 (d, 1H, J = 13 Hz), 4.11- 4.19 (m, 3 H), 3.59 - 3.77 (m, 4H), 3.03 - 3.18 (m, 3H), 2.86 (t, 1H, J = 8.0 Hz), 2.50 - 2.77 (m, 4H), 1.88 - 1.90 (m, 2H), 1.44 - 1.65 (m, 2H), 1.26 (t, 3H, J = 7.0 Hz), complete NMR, Spectrum (ESI) m/e = 439 (M+1).

15

EXAMPLE 2



1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethylpyrrolidine

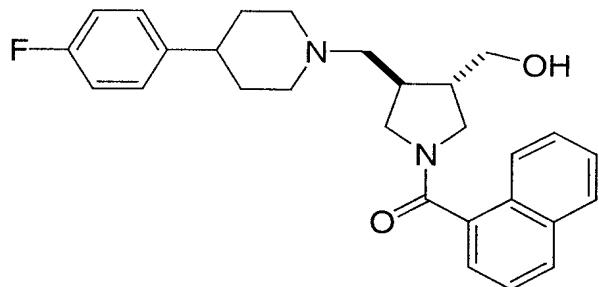
20

To a solution of 6.4 g (14.6 mmol) of 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(RS)-(ethoxycarbonyl)pyrrolidine in 60 mL of THF at 0 °C was added 17.5 mL (17.5 mmol) of a 1M solution of lithium aluminum hydride (LAH) in ether and the reaction was stirred at 0 °C for 30 min. The reaction

mixture was quenched with 5N NaOH. The reaction mixture was extracted with ether and the combined organic fractions were washed with 5N NaOH solution. The organic fractions were dried over Na₂SO₄, filtered and the filtrate was purified by chromatography [silica, hexanes: ethyl acetate: (2N NH₃ in MeOH), 10: 10: 1] to give 5 4.7 g of the title compound. Spectrum (ESI) m/e = 383 (M+1). ¹H NMR (CDCl₃) δ c7.31 - 7.33 (m, 4 H), 7.26 - 7.28 (m, 1H), 7.16 - 7.19 (m, 2H), 6.97 (t, 2H, J = 8.5 Hz), 3.63 - 3.66 (m, 2H), 3.57 (d, 1H, J = 13Hz), 3.43 (t, 1H, J = 10 Hz), 3.22 (d, 1H, J = 11 Hz), 2.97 (d, 1H, J = 11 Hz), 2.80 (d of d, 1H, J = 8.5, 7.5 Hz), 2.76 (t, 1H, J = 9 Hz), 2.12 - 2.54 (m, 8 H), 2.02 (t of d, 1H, J = 2.5, 12 Hz), 1.75 - 1.85 (m, 5H).

10

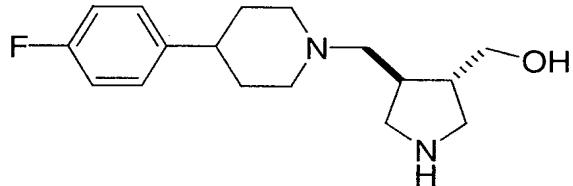
EXAMPLE 3



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxyethylpyrrolidine

15

Step 1. 3-(RS)-(4-(4-Fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxyethylpyrrolidine

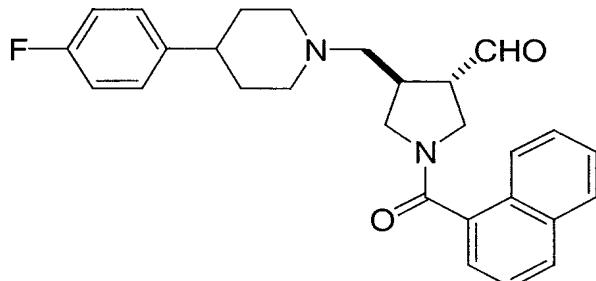


20 A mixture of 0.89 g (2.3 mmol) of 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxyethylpyrrolidine, 2.9 g (17.7 mmol) of ammonium formate and 0.39 g of Pearlman's catalyst [Pd(OH)₂/C] in 30 mL of MeOH was stirred at 70 °C for 1 h. The reaction mixture was filtered through a thin pad of Celite and the filtrate was concentrated to give 0.7 g of the title compound.

Step 2. 1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinyl-methyl)-164-(SR)-hydroxyethylpyrrolidine

To a solution of 0.63 g (2.15 mmol) of 3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxyethylpyrrolidine and 0.6 mL (4.3 mmol) of Et₃N in 5 20 mL of CH₂Cl₂ at 0 °C was added 0.32 mL (2.15 mmol) of 2-naphthoyl chloride and the reaction mixture was stirred for 1.2 h. To the reaction mixture was added 0.5 mL of MeOH and the reaction mixture was stirred 18 h at rt. The reaction mixture was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1:2 to 1:1) to give 0.63 g of the title compound. ¹H NMR (CDCl₃) δ 7.85 - 10 7.91 (m, 3H), 7.45 - 7.58 (m, 4H), 7.14 - 7.20 (m, 2 H), 6.96 - 7.00 (m, 2H) ; Mass Spectrum (ESI) m/e = 447 (M+1).

EXAMPLE 4



15

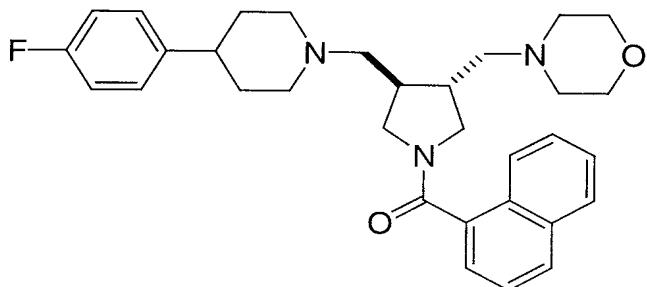
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine

To a solution of 0.1 mL (1.2 mmol) of oxalyl chloride in 10 mL of CH₂Cl₂ at -78 °C was added 0.17 mL (2.37 mmol) of DMSO and the reaction 20 mixture was stirred for 10 min. To this reaction mixture at -78 °C was added a solution of 0.26 g (0.59 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethylpyrrolidine in 10 mL of CH₂Cl₂. After stirring for 10 min. at -78 °C, 0.41 mL (2.9 mmol) of Et₃N was added and the reaction was allowed to warm to rt. The reaction mixture was poured into 25 ether and washed twice with sat'd NaHCO₃ solution and once with sat'd NaCl solution. The organic fraction was dried over Na₂SO₄, filtered and the filtrate was concentrated to give 0.29 g of the title compound. ¹H NMR (CDCl₃) δ 9.85, 9.70 (d,

1H, J = 2.0 Hz), 7.86 - 7.91 (m, 2H), 7.48 - 7.55 (m, 3H), 7.10 - 7.18 (m, 2H), 6.94 - 7.00 (m, 2H); Mass Spectrum (ESI) m/e = 445 (M+1).

EXAMPLE 5

5

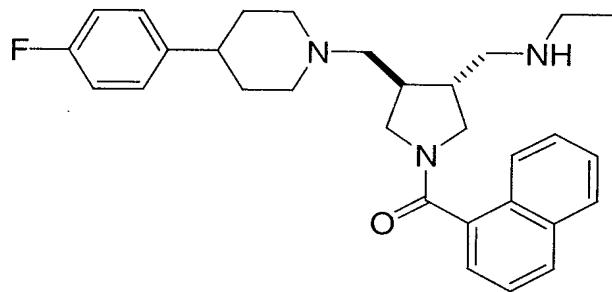


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(1-morpholinomethyl)pyrrolidine

To a solution of 0.03 g (0.073 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine and 0.013 mL (0.145 mmol) of morpholine in 2 mL of dichloroethane at rt was added 0.046 g (0.27 mmol) of sodium triacetoxyborohydride. After stirring for 1.5 h at rt, the reaction mixture was partitioned between CH_2Cl_2 and sat'd NaHCO_3 . The organic fraction was dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, CH_2Cl_2 : MeOH, 95: 5) to give the title compound.

^1H NMR (CDCl_3) δ (complete) 7.87 - 7.90 (m, 3H), 7.45 - 7.55 (m, 4H), 7.17 - 7.20, 7.08 - 7.11 (m, 2H), 7.00, 6.95 (t, 2H, J = 9.0 Hz), 4.03 - 4.09 (m, 1H), 3.72 (t, 2H, J = 4.5 Hz), 3.60 - 3.64 (m, 1H), 3.56 (t, 2H, J = 4.5 Hz), 2.97 - 3.06 (m, 2H), 2.82 - 2.88 (m, 1H), 2.43 - 2.55 (m, 4H), 2.24 - 2.43 (m, 5H), 2.09 - 2.19 (m, 3H), 1.49 - 1.98 (m, 5H); Mass Spectrum (ESI) m/e = 516 (M+1).

EXAMPLE 6

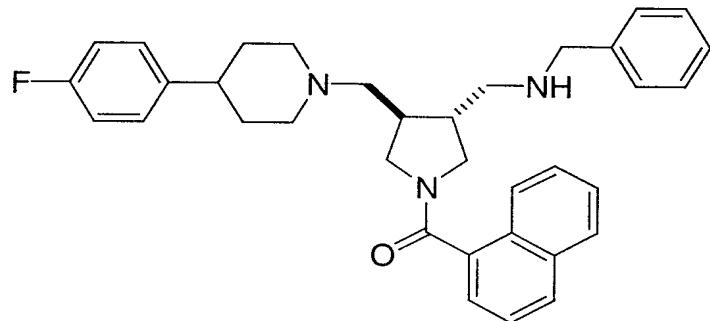


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(ethylaminomethyl)pyrrolidine

The title compound was prepared as described in Example 5.

5 Mass Spectrum (ESI) m/e = 474 (M+1).

EXAMPLE 7



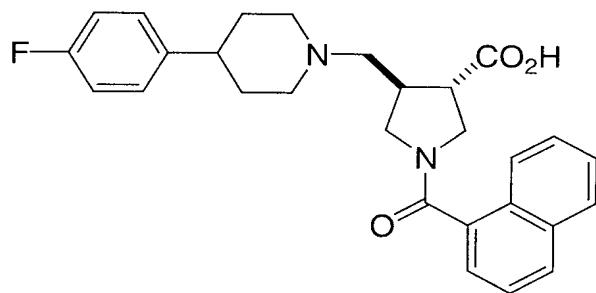
10 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(benzylaminomethyl)pyrrolidine

The title compound was prepared as described in Example 5.

Mass Spectrum (ESI) m/e = 536 (M+1).

15

EXAMPLE 8



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-carboxypyrrolidine

A mixture of 0.126 g (0.28 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethyl pyrrolidine, 0.18 g (0.85 mmol) of NaIO4, and 0.0029 g (0.014 mmol) of RuCl3.3 H2O in 2 mL of CCl4, 3 mL of H2O and 2 mL of CH3CN was stirred at rt for 1 h. The reaction mixture was partitioned between CH2Cl2 and H2O. The organic fraction was dried over Na2SO4, filtered and the filtrate was concentrated to give the title compound. ¹H NMR (key peaks) (CDCl3) δ 7.81 - 7.88 (m, 3H), 7.43 - 7.74 (m, 4H), 7.11 - 7.14 (m, 2H), 6.97 (t, 2H, J = 8.0 Hz), Mass Spectrum (ESI) m/e = 461 (M+1).

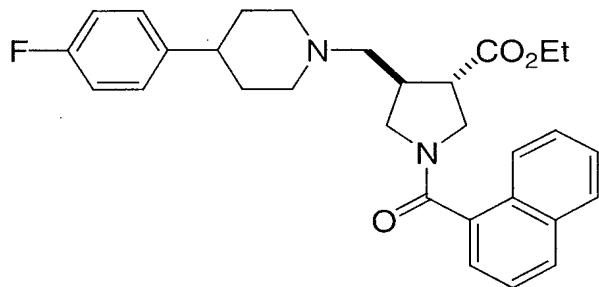
EXAMPLE 9

15 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-methoxycarbonylpiperidinylmethylpyrrolidine

To a solution of 0.037 g (0.08 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-carboxypiperidinylmethylpyrrolidine in 0.6 mL of MeOH and 1.2 mL of THF at rt was added 0.2 mL (0.4 mmol) of TMSCHN2 (2M in hexanes) and the reaction mixture was stirred for 6 h. The reaction mixture was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1:3) to give the title compound. ¹H NMR (CDCl3) δ (key peaks) 7.87 - 7.91 (m, 3H), 7.47 - 7.56 (m, 4H), 7.15 - 7.18 and 7.08-7.11 (m, 2H), 6.98 and 6.95 (t, 2H, J = 8.5 Hz), 3.79 and 3.62 (s, 3H); Mass Spectrum (ESI) m/e = 475 (M+1).

25

EXAMPLE 10



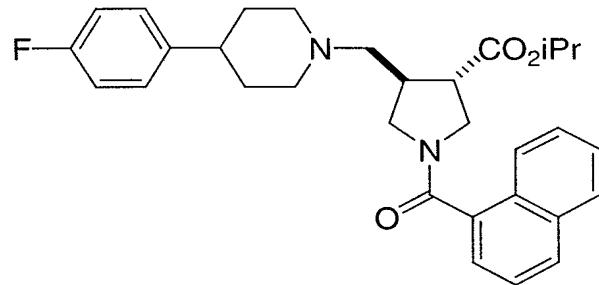
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-ethoxycarbonylpyrrolidine

To a solution of 0.026 g (0.057 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-carboxypyrrolidine, 0.03 g (0.114 mmol) of BOP-Cl and 0.032 mL (0.228 mmol) of Et₃N in 2 mL of CH₂Cl₂ at rt was added 0.013 mL (0.228 mmol) of EtOH and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated and the residue purified by chromatography (silica, acetone: hexanes, 1:2) then by HPLC (silica, Waters RCM 25x100 with (0.1% 5 iPr₂NH in methyl tbutyl ether) : hexane = 4.5 :5.0 to give the title compound.

10 ¹H NMR (CDCl₃) δ (key peaks) 7.88 - 7.91 (m, 3H), 7.47 - 7.57 (m, 4H), 7.16 - 7.19 and 7.09 - 7.12 (m, 2H), 6.99 and 6.96 (t, 2H, J = 8.5 Hz), 1.34 and 1.21 (t, 3H, J = 7.0 Hz); Mass Spectrum (ESI) m/e = 489 (M+1).

15

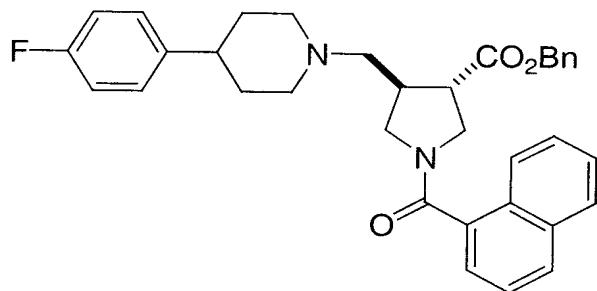
EXAMPLE 11



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-isopropoxycarbonylpyrrolidine

20 The title compound was prepared as described in Example 10. Mass Spectrum (ESI) m/e = 503 (M+1).

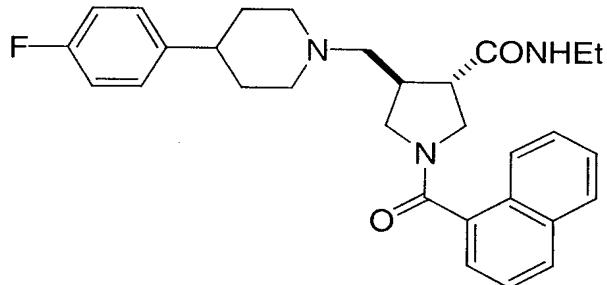
EXAMPLE 12



5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-benzyloxycarbonylpyrrolidine

The title compound was prepared as described in Example 10. ¹H NMR (CDCl₃) δ (key peaks) 7.88 - 7.91 (m, 3 H), 7.45 - 7.56 (m, 3H), 7.27 - 7.41 (m, 5 H), 7.08 - 7.16 (m, 2H), 6.99 and 6.96 (t, 2H, J = 9.0 Hz), 5.26 and 5.12 (d, 1H, J = 12.5 Hz), 5.22 and 5.06 (d, 1H, J = 12.5 Hz); Mass Spectrum (ESI) m/e = 551 (M+1).

EXAMPLE 13



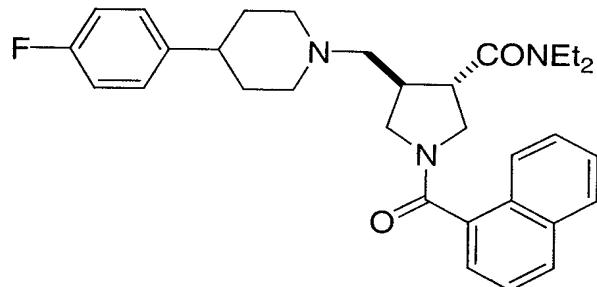
15

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N-ethylaminocarbonyl)pyrrolidine

To a solution of 0.037 g (0.08 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-carboxypyrrolidine and 0.06 mL (0.12 mmol) of ethylamine in 2 mL of CH₂Cl₂ at rt was added 0.031 g (0.12 mmol) of BOPCl Bis(2-oxo-3-oxazolidinyl)phosphinic chloride, Aldrich) and 0.045 mL Et₃N and the

reaction mixture was stirred for 18 h. The reaction mixture was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1: 2) to give the title compound. ^1H NMR (CDCl_3) δ (key peaks) 7.85 - 7.90 (m, 3H), 7.45 - 7.56 (m, 4H), 7.09 - 7.19 (m, 2H), 6.96 - 7.03 (m, 2H), 3.94 - 4.49 (m, 4H); Mass Spectrum (ESI) m/e = 488 (M+1).

EXAMPLE 14

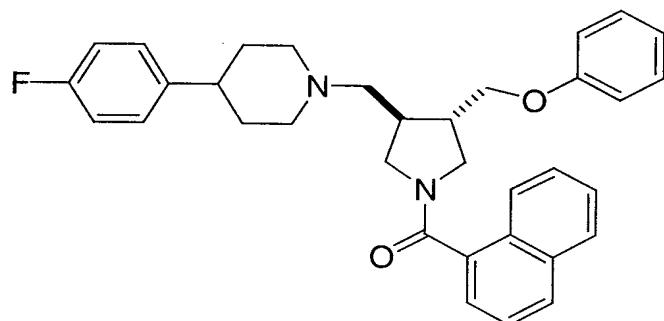


10 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N, N-diethylaminocarbonyl)pyrrolidine

The title compound was prepared as described in Example 13. Mass Spectrum (ESI) m/e = 516 (M+1).

15

EXAMPLE 15

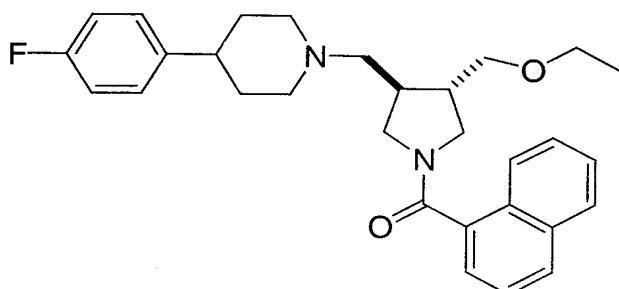


1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(phenoxyethyl)pyrrolidine

A solution of 0.062 g (0.14 mmol) of Ph₃Bi (Aldrich) in 1 mL of CH₂Cl₂ and 0.65 mL of THF at rt was added 0.027 mL (0.18 mmol) of trifluoroacetic acid and the reaction mixture was stirred for 10 min. This solution was added to a solution of 0.046 g (0.1 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethylpyrrolidine in 1 mL of CH₂Cl₂.
 5 To this reaction mixture was added 0.0083 g (0.046 mmol) of Cu(OAc)₂ and the reaction mixture was stirred at 40 °C for 72 h. The reaction mixture was filtered through a thin pad of silica (acetone: hexanes, 1:2) and the filtrate was concentrated. The residue was purified by chromatography (silica, Waters RCM 25x100 with (0.1%
 10 iPr₂NH in methyl tbutyl ether) : hexane = 2.25:7.0) to give the title compound. ¹H NMR (CDCl₃) δ (key peaks) 7.88 -7.92 (m, 3H), 7.47 - 7.56 (m, 4H), 7.23 - 7.34 (m, 2H), 7.07 - 7.18 (m, 2H), 6.92 - 7.01 (m, 4H), 6.80 (d, 1H, J = 7.5 Hz), 5.12 (S, 2H). Mass Spectrum (ESI) m/e = 523 (M+1).

15

EXAMPLE 16



1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S,R)-(ethoxymethyl)pyrrolidine

20 To a solution of 0.033 g (0.074 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethylpyrrolidine and 0.057 g (0.22 mmol) of AgOTf in 2 mL of CH₂Cl₂ was added 0.058 mL (0.26 mmol) of 2,6-di-t-butylpyridine and 0.019 mL (0.24 mmol) of ethyl iodide and the reaction mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with CH₂Cl₂ and filtered
 25 through a thin pad of Celite eluting with acetone: hexanes (1: 2). The filtrate was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1: 3 to 1: 2) to give the title compound. ¹H NMR (CDCl₃) δ (key peaks) 7.88 - 7.91 (M, 3H), 7.47 - 7.57 (M, 4H), 7.09-7.12 and 7.18 - 7.21 (M, 2H),

7.01 and 6.96 (t, 2H, J = 8.5 Hz), 1.25 and 1.09 (t, 3H, J = 7.0 Hz); Mass Spectrum (ESI) m/e = 475 (M+1).

EXAMPLE 17

5

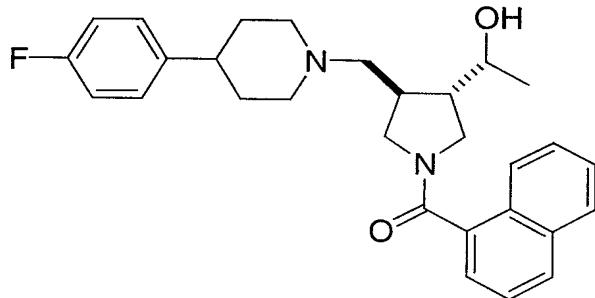
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(methoxymethyl)pyrrolidine

A solution of 0.025 g (0.057 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethylpyrrolidine, 0.013 g (0.23

10 mmol) of KOH and 0.028 mL (0.46 mmol) of methyl iodide in 2 mL of DMSO was stirred at rt for 1.2 h. The reaction mixture was poured into ether and washed with sat'd NaHCO₃ and NaCl solutions, dried over Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1:2) to give the title compound. Mass Spectrum (ESI) m/e = 461 (M+1).

15

EXAMPLE 18



20 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxyethyl)pyrrolidine (diastereomers 1 and 2)

To a solution of 0.03 g (0.67 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine in 6 mL of THF at 0 °C was added 1.34 mL (1.34 mmol) of MeMgBr (1M in THF). The reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was quenched with sat'd NaHCO₃ solution. The organic fraction was filtered through a thin pad of Celite. The filtrate was concentrated and purified by chromatography (silica, hexanes: ethyl

acetate: EtOH, 10: 10: 1) to give 0.05 g of diastereomer #1 and 0.16 g of diastereomer #2.

Diastereomer #1

5 ^1H NMR (CDCl_3) δ (key peaks) 7.86 - 7.91 (m, 3H), 7.46 - 7.58 (m, 4H), 7.13 - 7.19 (m, 2H), 6.94 - 7.00 (m, 2H), 1.30 and 0.90 (d, 3H, $J = 6.0$ Hz); Mass Spectrum (ESI) m/e = 461 (M+1).

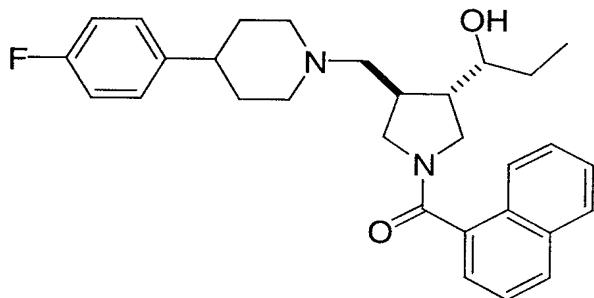
Diastereomer #2

10 ^1H NMR (CDCl_3) δ (key peaks) 7.84- 7.90 (m, 3H), 7.44 - 7.56(m, 4H), 7.12 - 7.18 (m, 2H), 6.94 - 6.98 (m, 2H), 1.24 and 1.03 (d, 3H, $J = 6.5$ Hz) Mass Spectrum (ESI) m/e = 461 (M+1).

The following Examples 19 to 24 were prepared from 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine and the corresponding Grignard reagent as described in Example 19.

15

EXAMPLE 19



20 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxypropyl)pyrrolidine

Diastereomer #1

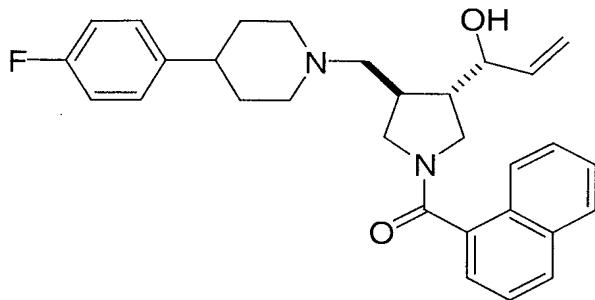
Mass Spectrum (ESI) m/e = 475 (M+1).

Diastereomer #2

Mass Spectrum (ESI) m/e = 475 (M+1).

25

EXAMPLE 20



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxy-2-propenyl)pyrrolidine

Diastereomer #1

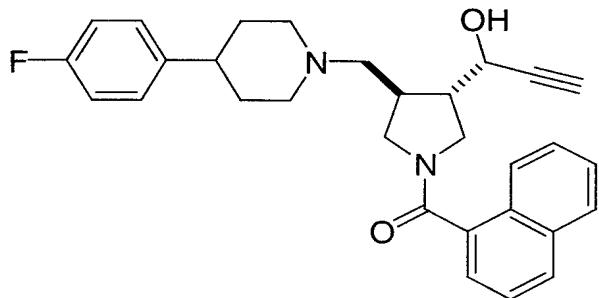
5 Mass Spectrum (ESI) m/e = 473 (M+1).

Diastereomer #2

Mass Spectrum (ESI) m/e = 473 (M+1).

EXAMPLE 21

10

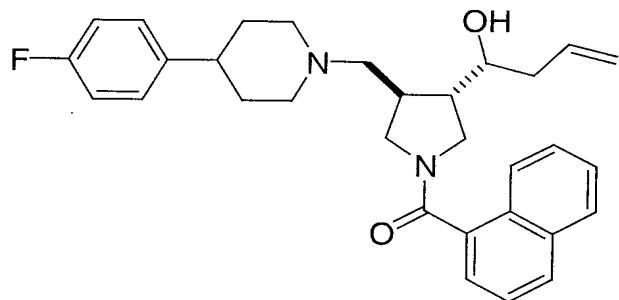


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxy-2-propynyl)pyrrolidine

Mass Spectrum (ESI) m/e = 471 (M+1).

15

EXAMPLE 22



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxy-3-butene)pyrrolidine

Diastereomer #1

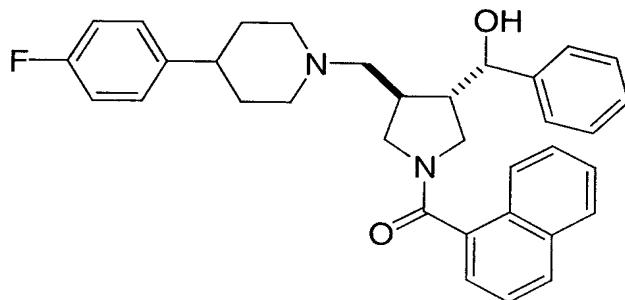
5 Mass Spectrum (ESI) m/e = 487 (M+1).

Diastereomer #2

Mass Spectrum (ESI) m/e = 487 (M+1).

EXAMPLE 23

10



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(phenylhydroxymethyl)pyrrolidine

Diastereomer #1

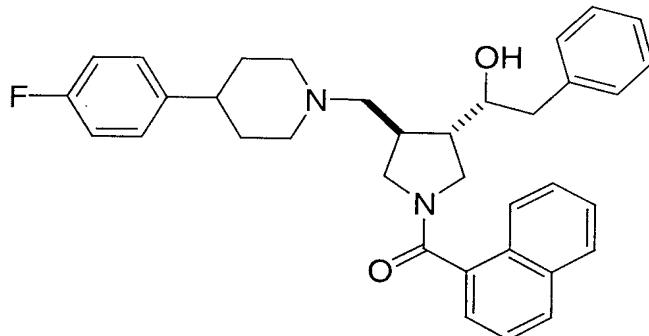
15 Mass Spectrum (ESI) m/e = 523 (M+1).

Diastereomer #2

Mass Spectrum (ESI) m/e = 523 (M+1).

EXAMPLE 24

20

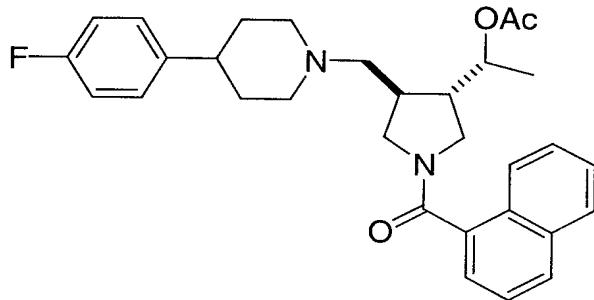


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-phenyl-1-hydroxyethyl)pyrrolidine

Mass Spectrum (ESI) m/e = 537 (M+1).

5

EXAMPLE 25



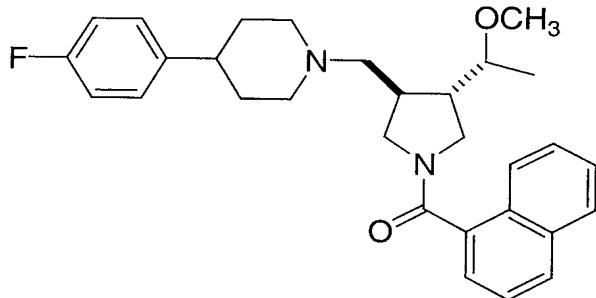
1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-acetoxyethyl)pyrrolidine

A solution of 0.026g (0.057 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxyethyl)pyrrolidine (diastereomer 2, Example 18), 0.027 mL (0.28 mmol) of acetic anhydride, 0.046 mL of pyridine and 3.4 mg of DMAP in 2 mL of THF was stirred at rt for 18 h. The reaction mixture was concentrated and purified by chromatography (silica, hexanes: ethylacetate: (2N NH₃ in MeOH), 15: 15: 1) to give the title compound as white solid.

¹H NMR (CDCl₃) δ (key peaks) 7.89- 7.90 (m, 3H), 7.47 - 7.54 (m, 4H), 7.19 and 7.09 (d of d, 2H, J = 6.0, 8.5 Hz), 6.99 and 6.94 (t, 2H, J = 8.5 Hz), 5.04 - 5.20 (m, 1H), 1.34 and 1.09 (d, 3H, J = 6.5 Hz), Mass Spectrum (ESI) m/e = 503 (M+1).

20

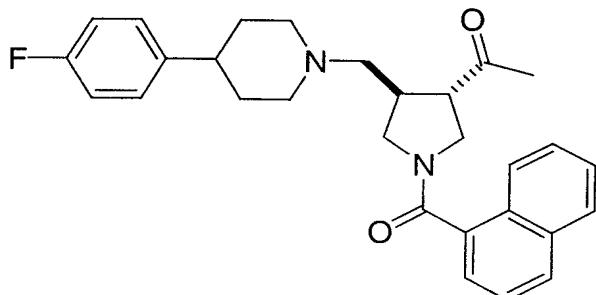
EXAMPLE 26



5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-methoxyethyl)pyrrolidine

A solution of 0.026g (0.057 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxyethyl)pyrrolidine (diastereomer 2), 0.012 mg (0.23 mmol) of KOH and 0.0042 mL (0.068 mmol) of methyliodide in 1 mL of DMSO was stirred at rt for 30 min. The reaction mixture was diluted with ether and washed with sat'd NaHCO₃ and NaCl solutions. The organic fraction was dried over Na₂SO₄, filtered and the filtrate was concentrated and purified by chromatography (silica, hexanes: ethylacetate: (2N NH₃ in MeOH), 10: 10: 1) to give the title compound. ¹H NMR (CDCl₃) δ (key peaks) 7.88-7.91(m, 3H), 7.45 - 7.55 (m, 4H), 7.20 and 7.10 (d of d, 2H, J = 5.5, 8.5 Hz), 7.00 and 6.95 (t, 2H, J = 9.0 Hz), 3.40 and 3.24 (s, 3H) 1.25 and 1.02 (d, 3H, J = 6.5 Hz), Mass Spectrum (ESI) m/e = 475 (M+1).

EXAMPLE 27

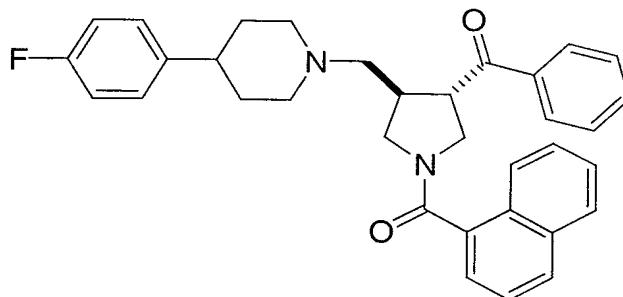


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-acetylpyrrolidine

5 The title compound was prepared from 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxyethyl)pyrrolidine according to procedures described in Example 4. ^1H NMR (CDCl_3) δ (key peaks) 7.86 - 7.91 (m, 3H), 7.44 - 7.57 (m, 4H), 7.08 - 7.16 (m, 2H), 6.93 - 6.99 (m, 2H), 2.34 and 2.17 (s, 3H); Mass Spectrum (ESI) m/e = 459 (M+1).

EXAMPLE 28

10



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-benzoylpyrrolidine

15 The title compound was prepared from 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(phenylhydroxymethyl) pyrrolidine according to procedures described in Example 4. ^1H NMR (CDCl_3) δ (key peaks) 8.14 (d, 1H, J = 7.5 Hz), 7.97 - 8.01 (m, 2H), 7.42 - 7.63 (7H), 6.93 - 7.01 (m, 4H), Mass Spectrum (ESI) m/e = 521 (M+1).

20

EXAMPLE 29

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1-hydroxy-1-methylethyl)pyrrolidine

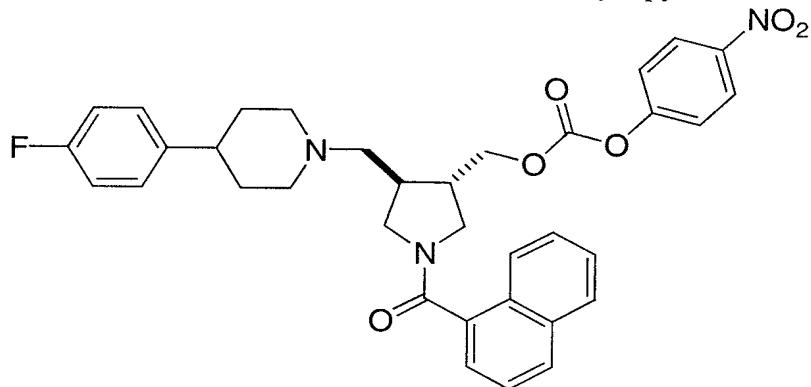
25 To a solution of 0.03 g (0.065 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-acetylpyrrolidine in 20 mL of THF at rt was added 0.19 mL (0.195 mmol) of MeMgBr (1M in THF) and the reaction mixture was stirred for 30 min. The reaction mixture was partitioned between CH_2Cl_2 and

NaHCO₃. The organic fraction was filtered through a thin pad of Celite and the filtrate was concentrated. The residue was purified by chromatography (silica, MeOH: CH₂Cl₂, 2: 98) to give the title compound. ¹H NMR (CDCl₃) δ (key peaks) 7.88 - 7.89 (m, 3H), 7.45 - 7.57 (m, 4H), 7.13 - 7.19 (m, 2H), 6.94 - 6.99 (m, 2H), 5 1.31 and 1.08 (s, 3H), 1.25 and 0.91 (s, 3H); Mass Spectrum (ESI) m/e = 475 (M+1).

EXAMPLE 30

10 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N-ethylcarbamoyloxymethyl)pyrrolidine

Step 1. 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-nitrophenoxy carbonyloxymethyl)-pyrrolidine



15 A solution of 0.1 g (0.225 mmol) of 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-4-(nitrophenoxy carbonyl oxymethyl)pyrrolidine, 0.055 g (0.45 mmol) of DMAP, 0.094 mL (0.68 mmol) of Et₃N and 0.082 g (0.41 mmol) of 4-nitrophenylchloroformate in 4 mL of CH₂Cl₂ was stirred at rt for 16 h. The reaction mixture was concentrated and the title compound 20 was used without further purification.

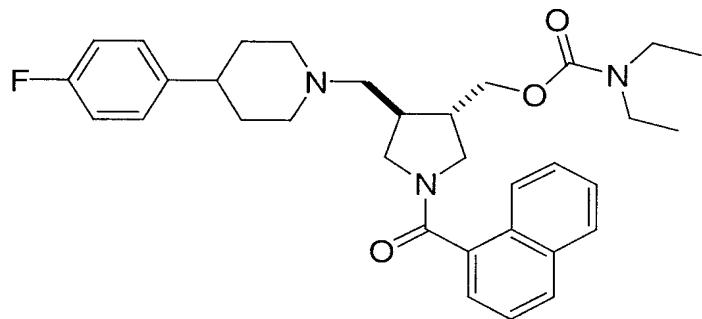
Step 2. A solution of 0.045 g (0.075 mmol) of 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N-ethylcarbamoyl oxymethyl)pyrrolidine and 0.23 mL (0.45 mmol) of ethylamine in 2 mL of CH₂Cl₂ was stirred at rt for 2 h.

25 The reaction mixture was diluted with ether and washed twice with 2N NaOH solution. The organic fraction was dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone: hexanes,

1: 3) to give the title compound. ^1H NMR (CDCl_3) δ (key peaks) 7.85 - 7.91 (m, 3H), 7.45 - 7.56 (m, 4H), 7.08 - 7.20 (m, 2H), 6.93 - 7.01 (m, 2H), 1.17 (t, 3H, J = 7.0 hz); Mass Spectrum (ESI) m/e = 518 (M+1).

5

EXAMPLE 31

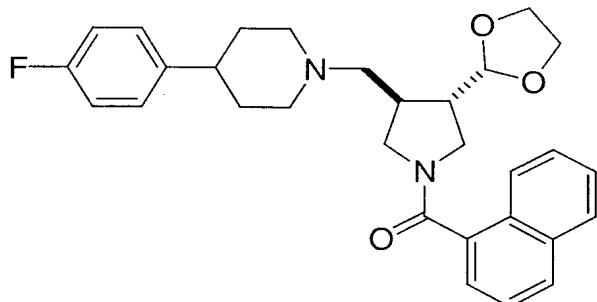


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N,N-diethylcarbamoyloxymethyl)pyrrolidine

10

The title compound was prepared as described in Example 30, using diethylamine. Mass Spectrum (ESI) m/e = 546 (M+1).

EXAMPLE 32



15

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine

Step 1. 1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine

The title compound was prepared from 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-hydroxymethylpyrrolidine according to 5 procedures described in Example 4.

Step 2. 1-(Benzyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine

A solution of 0.046 g (0.104 mmol) of 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine, 0.058 mL (1.04 mmol) of 10 ethyleneglycol and 0.047 g (0.25 mmol) of TsOH.H₂O in 5 mL of benzene was heated at reflux for 2 h. The reaction mixture was cooled to rt and diluted with ether. The reaction mixture was washed twice with sat'd NaHCO₃ solution, dried over 15 Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, MeOH: CH₂Cl₂, 5: 95) to give the title compound.

Step 3. 3-(RS)-(4-(4-Fluorophenyl)piperidinylmethyl)-4-(SR)-((1,3-dioxolan-2-yl)pyrrolidine

20 The title compound was prepared as described in Example 3, Step 1.

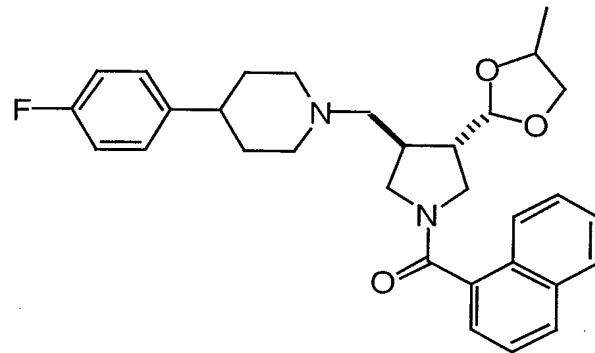
Step 4. 1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine

The title compound was prepared from 3-(RS)-(4-(4-fluoro 25 phenyl)piperidinylmethyl)-4-(S,R)-(1,3-dioxolan-2-yl)pyrrolidine and 2-naphthoylchloride as described in Example 3, Step 2. ¹H NMR (CDCl₃) δ (key peaks) 7.87 - 7.93 (m, 3H), 7.46 - 7.55 (m, 4H), 7.19 and 7.09 (d of d, 2H, J = 5.5, 8.5 Hz), 7.00 and 6.95 (t, 2H, J = 8.5 Hz), 5.03 and 4.85 (d, 1H, J = 3.5 Hz); Mass Spectrum (ESI) m/e = 489 (M+1).

30

The following Examples 34 to 36 were prepared from 1-(1-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine and the corresponding diol according to procedures described in Example 33.

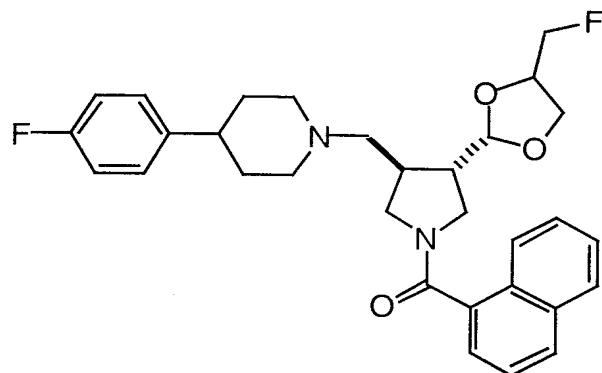
EXAMPLE 34



5 1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-methyl-1,3-dioxolan-2-yl)pyrrolidine

Mass Spectrum (ESI) m/e = 504 (M+1).

EXAMPLE 35



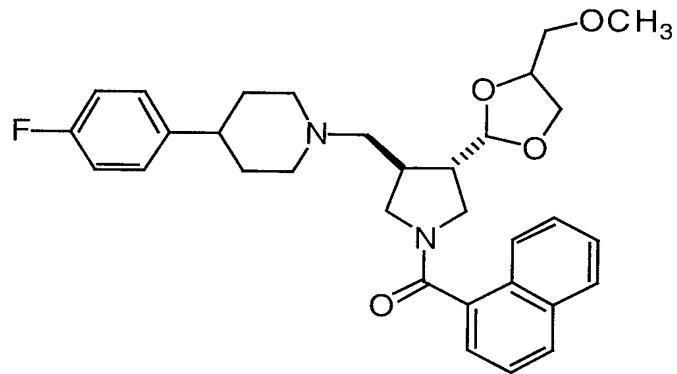
10

1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-fluoromethyl-1,3-dioxolan-2-yl)pyrrolidine

Mass Spectrum (ESI) m/e = 522 (M+1).

15

EXAMPLE 35

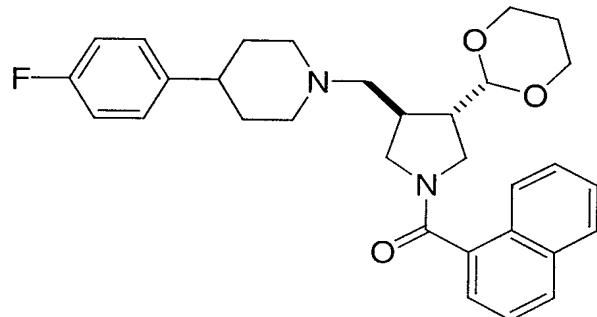


1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-methoxymethyl-1,3-dioxolan-2-yl)pyrrolidine

Mass Spectrum (ESI) m/e = 534 (M+1).

5

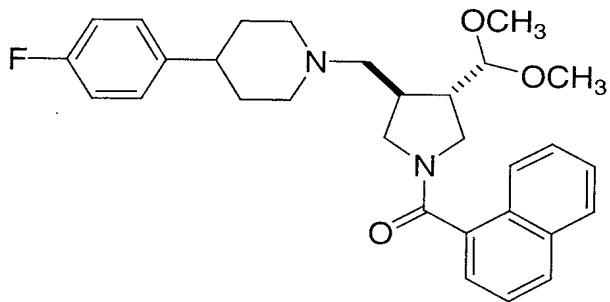
EXAMPLE 36



10 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxan-2-yl)pyrrolidine

Mass Spectrum (ESI) m/e = 503 (M+1).

EXAMPLE 37

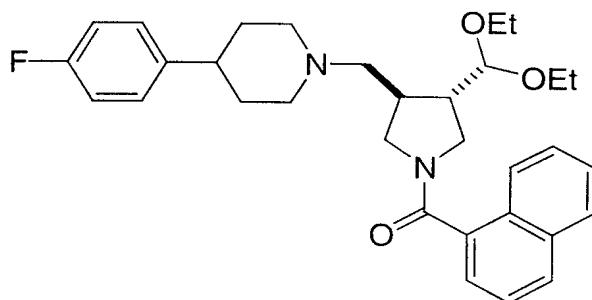


1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(S,R)-(1,1-dimethoxymethyl)pyrrolidine

5 A solution of 0.035 g (0.078 mmol) of 1-(2-naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(SR)-formylpyrrolidine, 0.085 mL (0.78 mmol) of trimethylorthoformate and 0.018 g (0.094 mmol) of TsOH.H₂O in 2 mL of MeOH was heated at reflux for 2 h. The reaction mixture was diluted with ether and washed twice with sat'd NaHCO₃ solution and NaCl solution. The organic fraction was dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by 10 chromatography [silica, ethyl acetate: hexanes: (2N NH₃ in MeOH), 10: 10: 1] to give the title compound. ¹H NMR (CDCl₃) δ (key peaks) 7.87 - 7.91 (m, 3H), 7.45 - 7.55 (m, 4H), 7.19 and 7.09 (d of d, 2H, J = 5.5, 9.0 Hz), 7.00 and 6.95 (t, 2H, J = 8.5 Hz), 4.38 and 4.27 (d, 1H, J = 6.0 Hz); Mass Spectrum (ESI) m/e = 491 (M+1).

15

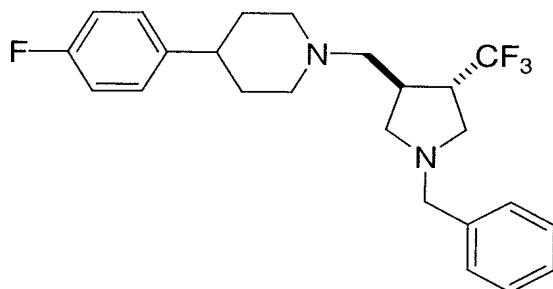
EXAMPLE 38



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(SR)-(1,1-diethoxymethyl)pyrrolidine

20 The title compound was prepared as described in Example 39 using triethylorthoformate. Mass Spectrum (ESI) m/e = 519 (M+1).

EXAMPLE 40

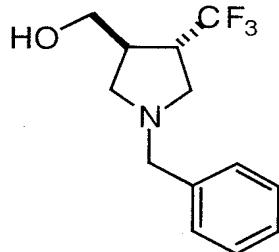


5 1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

Step 1. 1-Benzyl-3-(RS)-carboethoxy-4-(RS)-trifluoromethylpyrrolidine

The title compound (1.8 g) was prepared from ethyl-3-trifluoromethyl acrylate, and N-(methoxymethyl)-N-trimethylsilyl methylbenzylamine as described in Example 1, Step 2. ^1H NMR (CDCl_3) δ (complete) 7.27 - 7.42 (m, 5H), 4.20 (q, 2H, J = 7.0 Hz), 3.67 (d, 1H, J = 13 Hz), 3.61 (d, 1H, J = 13 Hz), 3.37 - 3.43 (m, 1H), 3.12 - 3.15 (m, 1H), 2.81-2.93 (m, 3H), 2.71 (d of d, 1H, J = 6, 10 Hz).

15 Step 2: 1-Benzyl-3-(RS)-hydroxymethyl-4-(RS)-trifluoromethyl pyrrolidine



To a solution of 1.8 g (6 mmol) of 1-benzyl-3-(RS)-carboethoxy-4-(RS)-trifluoromethylpyrrolidine in 20 mL of THF at 0 °C was added 4.8 mL (4.8 mmol) of a 1M solution of LAH in THF and the reaction was stirred at rt for 30 min.

20 The reaction mixture was quenched with 5N NaOH solution and extracted with ether. The combined organic fractions were washed with 2N NaOH solution and sat'd NaCl solution, dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone: hexanes, 1: 8) to give 1.5 g of the

title compound. ^1H NMR (CDCl_3) δ (key peaks) 7.28 - 7.37 (m, 5H), 3.76 (d of d, 1H, J = 3.5, 10.5 Hz), 3.63 (s, 2H), 3.62 (d of d, 1H, J = 5.0, 10.5 Hz), 3.11 (t, 1H, J = 9.0 Hz), 2.60 (t, 1H, J = 7.0 Hz), 2.45 - 2.49 (m, 1H), 2.42 (d of d, 1H, J = 7.5, 9.5 Hz).

5

Step 3: 1-Benzyl-3-(RS)-formyl-4-(RS)-trifluoromethylpyrrolidine



10 To a solution of 0.98 mL (11.2 mmol) of oxalyl chloride in 30 mL of CH_2Cl_2 at -78 °C was added 1.6 mL (22.4 mmol) of DMSO and the reaction mixture was stirred for 10 min. To this reaction mixture at -78 °C was added a solution of 1.46 g (5.6 mmol) of 1-benzyl-3-(RS)-hydroxymethyl-4-(RS)-trifluoromethylpyrrolidine in 10 mL of CH_2Cl_2 . After stirring for 10 min. at -78 °C, 15 3.9 mL (28 mmol) of Et_3N was added and the reaction was allowed to warm to rt. The reaction mixture was poured into ether and extracted twice with sat'd NaHCO_3 solution and once with sat'd NaCl solution. The organic fraction was dried over Na_2SO_4 , filtered and the filtrate was concentrated to give 1.46 g of the title compound.

20

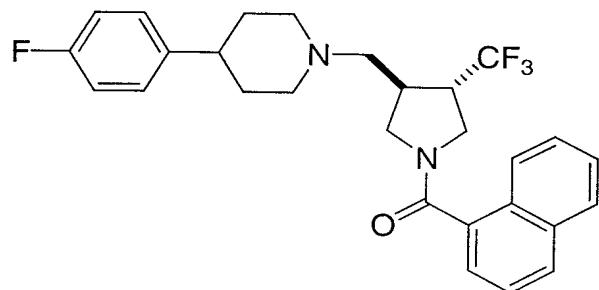
Step 4: 1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

25 To a solution of 1.46 g (5.6 mmol) of 1-benzyl-3-(RS)-formyl-4-(RS)-trifluoromethylpyrrolidine and 0.13 g (0.67 mmol) of 4-(4-fluorophenyl) piperidine (Example 1, Step 1) in 30 mL of dichloroethane at rt was added 2.37 g (11.2 mmol) of sodium triacetoxyborohydride. After stirring for 18 h at rt, the reaction mixture was partitioned between CH_2Cl_2 and sat'd NaHCO_3 . The organic fraction was dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone: hexanes, 1:8) to give 1.98 g of the title compound.

¹H NMR (key peaks) (CDCl₃) δ 7.28 - 7.37 (m, 5H), 7.19 - 7.22 (m, 2H), 7.01 (t, 2H, J = 8.5 Hz); Mass Spectrum (ESI) m/e = 421 (M+1).

EXAMPLE 41

5



1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

10 Step 1. 3-(RS)-(4-(4-Fluorophenyl)piperidinylmethyl)-4-(RS)-(trifluoromethyl)pyrrolidine

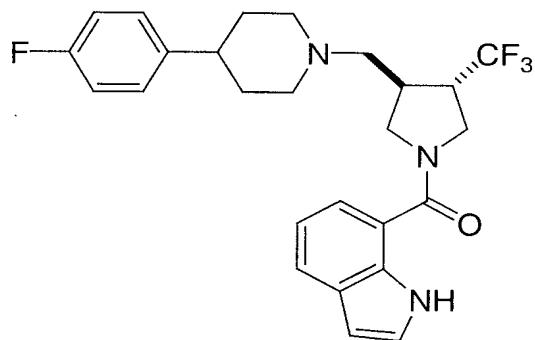
The title compound was prepared from 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine according to procedures described in Example 3.

15

Step 2. 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

20 The title compound was prepared from 3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(trifluoromethyl)pyrrolidine according to procedures described in Example 3, Step 2. ¹H NMR (key peaks) (CDCl₃) δ 7.17 - 7.20 (m, 2H), 6.99 (t, 2H, J = 8.5 Hz), Mass Spectrum (ESI) m/e = 331 (M+1).

EXAMPLE 42

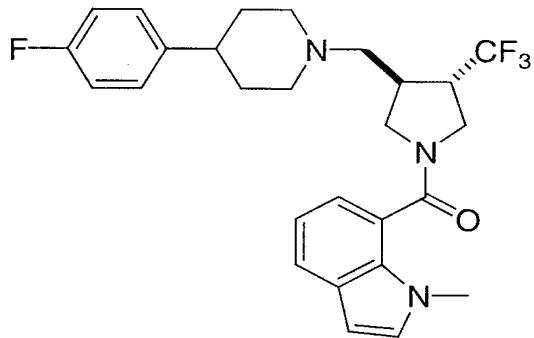


1-(7-Indolecarbonyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

A solution of 0.12 g (0.36 mmol) of 3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(trifluoromethyl)pyrrolidine, 0.069 g (0.43 mmol) of indole-7-carboxylic acid, 0.088 g (0.72 mmol) of DMAP and 0.097 g (0.5 mmol) of 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (Aldrich) in 10 mL of CH₂Cl₂ was stirred at rt for 4 h. The reaction mixture was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1: 5) to give the title compound. ¹H NMR (key peaks) (CDCl₃) δ 9.96 (s, 1H), 7.82 (d, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 7.5 Hz), 7.32 (t, 1H, J = 3.0 Hz), 7.17 - 7.21 (m, 3H), 7.03 (t, 2H, J = 8.5 Hz), 6.62 - 6.63 (m, 1H); Mass Spectrum (ESI) m/e = 474 (M+1).

EXAMPLE 43

15

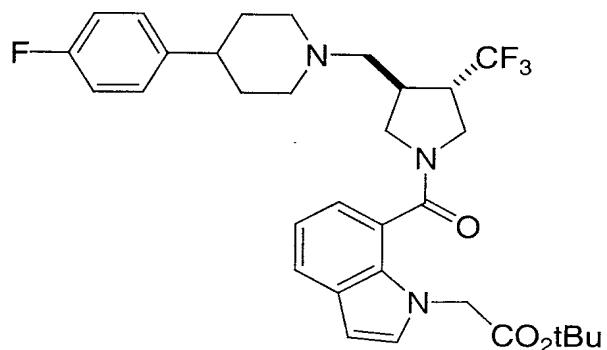


1-(1-Methyl-7-indolecarbonyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

To a solution of 0.033 g (0.07 mmol) of 1-(7-indolecarbonyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl) pyrrolidine and 0.022 g (0.084 mmol) of 18-Crown-6 ether in 2 mL of ether at rt was added 0.084 mL of KOt-Bu (1M in t-BuOH). After stirring for 5 min, 0.006 mL (0.098 mmol) of MeI 5 was added and the reaction was stirred for 1 h. The reaction mixture was concentrated and the residue was purified by chromatography (silica, acetone: hexanes, 1: 3) to give the title compound.

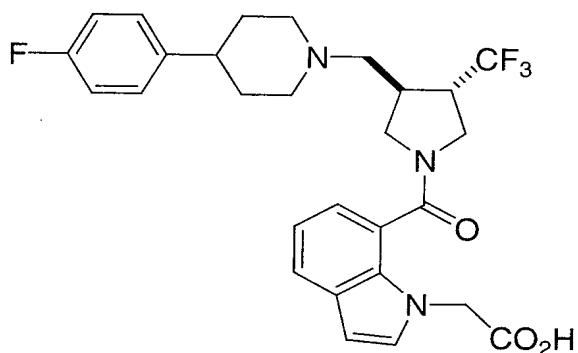
10 ^1H NMR (CDCl_3) δ (key peaks) 7.68 - 7.70 (m, 1H), 7.10 - 7.21 (m, 4H), 7.06 (t, 1H, J = 3.0 Hz), 6.97-7.03 (m, 2H), 6.55 (d, 1H, J = 3.0 hz); Mass Spectrum (ESI) m/e = 488 (M+1).

EXAMPLE 44



15 1-(1-t-Butoxycarbonylmethyl)-7-indolecarbonyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(trifluoromethyl)pyrrolidine

The title compound was prepared as described in Example 40 using t-butyldibromoacetate. Mass Spectrum (ESI) m/e = 588 (M+1).

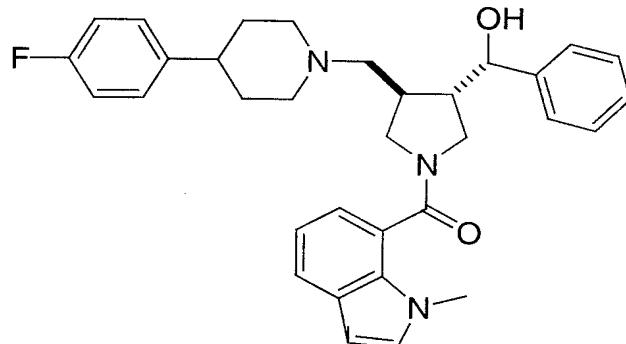


1-(1-Carboxymethyl)-7-indolecarbonyl-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl-4-(SR)-(trifluoromethyl)pyrrolidine

5 A solution of 0.036 g of 1-(1-t-butoxycarbonylmethyl)-7-indolecarbonyl-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl-4-(SR)-(trifluoromethyl)pyrrolidine and 0.05 mL of H₂O in 2 mL of TFA was stirred at rt for 40 min. The reaction mixture was concentrated and the residue was purified by chromatography (silica, CH₂Cl₂, MeOH, NH₃, 100: 10: 3) to give the title compound. Mass Spectrum (ESI) m/e = 532 (M+1).

10

EXAMPLE 46



15 1-(1-Methyl-7-indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl-4-(SR)-(phenylhydroxymethyl)pyrrolidine (diastereomers 1 and 2)

Step 1. 1-Benzyl-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl-4-(SR)-(phenylhydroxymethyl)pyrrolidine

The title compound was prepared from 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine according to procedures described in Example 18.

5 Step 2. 3-(RS)-(4-(4-Fluorophenyl)piperidinylmethyl)-4-(RS)-(phenylhydroxymethyl)pyrrolidine

The title compound was prepared from 1-benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(phenylhydroxymethyl)pyrrolidine as described in Example 3.

10

Step 3. 1-Methylindole-7-carboxylic acid

Step 3A. Benzylindole-7-carboxylate

A solution of 0.68 g (4.2 mmol) of indole-7-carboxylic acid, 0.9 g (8.4 mmol) of benzylalcohol 1.03 g (8.4 mmol) of DMAP and 1.6 g (8.4 mmol) of 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (Aldrich) in 30 mL of CH_2Cl_2 was stirred at rt for 18 h. The reaction mixture was concentrated and the residue was purified by chromatography (silica, hexanes: ethyl acetate 30:1) to give 0.88 g of the title compound.

20

Step 3B. Benzyl-1-methyl-7-indolecarboxylate

The title compound (0.15 g) was prepared from benzyl-7-indolecarboxylate according to procedures described in Example 40.

25

Step 3C. 1-Methyl-7-indolecarboxylic acid

The title compound (0.102 g) was prepared from benzyl-1-methyl-7-indolecarboxylate according to procedures described in Example 3.

30

Step 4. 1-(1-Methyl-7-indolecarbonyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(phenylhydroxymethyl)pyrrolidine

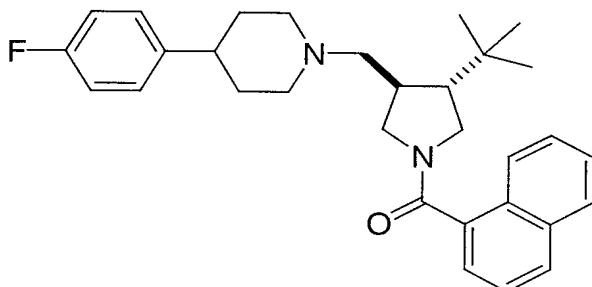
The title compound was prepared from 3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(phenylhydroxymethyl)pyrrolidine and 1-methyl-7-indolecarboxylic acid according to procedures described in Example 39. The crude product was purified by chromatography (silica, acetone :hexane = 1:2) to give the separate diastereomers of the title compound.

Diastereomer #1 Mass Spectrum (ESI) m/e = 526 (M+1).

Diastereomer #2 Mass Spectrum (ESI) m/e = 526 (M+1).

EXAMPLE 47

5



1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(t-butyl)pyrrolidine

10 Step 1. methyl-3-t-butylacrylate
 To a solution of 22.8 g (125 mmol) of trimethylphosphonoacetate in 25 mL of THF at -20 °C was added 125 mL (125 mmol) of a solution of sodium bis(trimethylsilyl)amide (1 M) in THF. After stirring for 20 min, 7.7 g (90 mmol) of trimethylacetaldehyde and the reaction mixture was stirred at -20 °C for 2 h. The reaction mixture was partitioned between H₂O and ether. The organic fraction was washed with H₂O, and sat'd NaCl solution, dried over MgSO₄, and filtered. The filtrate was concentrated to give the title compound which was used without further purification.

15 Step 2. N-allyl-N-(trimethylsilylmethyl)amine
 To 118 mL (1.57 mol) of allylamine warmed at 40 °C in an inert atmosphere was very slowly added 100 mL (0.72 mol) of chloromethyl trimethylsilane (approximate rate of 1 mL/min). The reaction mixture was slowly warmed to 70 °C and stirred for 24 h. The reaction mixture was cooled to 0 °C and to 20 it was added water to break up the gel and then 300 mL of 2N NaOH solution. The reaction mixture was extracted with ether. The combined organic fractions were washed with 500 mL of sat'd NaCl solution, dried over Na₂SO₄, filtered and the

filtrate was concentrated. The residue was purified by distillation (bp 80 - 84 °C @ 100 torr) to give 75 g of the title compound.

Step 3. N-Allyl-N-(methoxymethyl)-N-trimethylsilylmethyl)amine

5 To 75 g (0.57 mol) of N-allyl-N-(trimethylsilylmethyl)amine at 0 °C was slowly added 67 mL (0.88 mol) of aqueous formaldehyde (37%w/w). After stirring for 5 min, 65 mL (1.6 mol) of methanol was added followed by the addition of 94 g (0.68 mol) of K₂CO₃. The reaction mixture was warmed to rt and stirred for 12 h. The reaction mixture was partitioned between 300 mL of water and 300 mL of 10 ether. The organic fraction was washed with water and sat. NaCl solution. The combined aqueous fractions were extracted with ether. The combined organic fractions were dried over Na₂SO₄, filtered and the filtrate was concentrated to give 89 g of the title compound which was used without further purification.

15 Step 4. 1-Allyl-3-(SR)-carbomethoxy-4-(RS)-t-butylpyrrolidine

C

H

20 To a solution of 7.1 g (50 mmol) of methyl-3-t-butylacrylate, 18.7 g (100 mmol) of N-allyl-N-(methoxymethyl)-N-trimethyl silylmethyl)amine in 150 mL of CH₂Cl₂ at 0 °C was added 0.8 mL (10 mmol) of trifluoroacetic acid and the reaction mixture was stirred for 4 h while warming to rt. The reaction mixture was diluted with sat'd NaHCO₃ and extracted twice with 100 mL of ether. The combined organic fractions were washed with sat'd NaHCO₃ and NaCl solutions, dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was filtered through a 25 thin pad of silica, eluting with acetone: hexanes (3:7) to give 6.7 g of the title compound.

Mass Spectrum (ESI) m/e = 226 (M+1).

Step 5. 1-Allyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-t-butylypyrrolidine

The title compound was prepared as described in Example 37.

10 ^1H NMR (CDCl_3) δ 7.19 (m, 2H), 6.98 (t, 8.7 Hz, 2H), 5.94 (m, 1H), 5.21 (d of d, 1.8 Hz, 7.2 Hz, 1H), 5.11 (d of d, 0.9Hz, 10Hz, 1H), 3.14 (m, 2H), 2.97 (m, 2H), 2.79 (m, 2H), 2.48 (m, 2H), 2.29 (m, 2H), 2.22 (m, 1H), 2.19 - 2.05 (m, 3H), 1.92 (m, 1H), 1.82 - 1.64 (m, 4H), 1.55 (m, 1H), 0.90 (s, 9H); Mass Spectrum (ESI) m/e = 359 (M+1).

15 Step 6. 3-(SR)-(4-(4-Fluorophenyl)piperidinylmethyl)-4-(RS)-t-butylypyrrolidine

A mixture of 1 g (2.7 mmol) of 1-allyl-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-t-butylypyrrolidine and 0.13 g (0.14 mmol) of Wilkinson's catalyst [$\text{Rh}(\text{PPh}_3)_3\text{Cl}$] in 40 mL of an 85% solution of CH_3CN and water was heated to 90 °C and stirred for 3 h. The reaction mixture was cooled to rt and concentrated. The residue was partitioned between EtOAc and water. The organic fraction was washed with sat. NaHCO_3 , dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, CHCl_3 : MeOH : NH_3 , 90: 10:1) to give 0.75 g of the title compound.

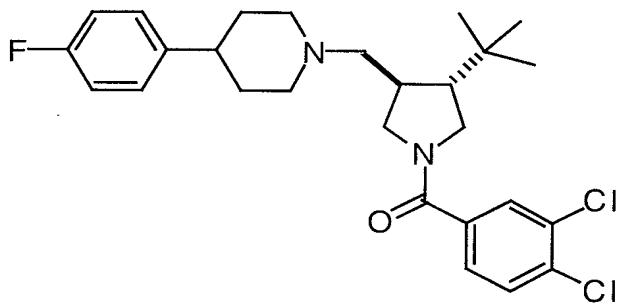
20

Step 6. 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinyl-methyl)-4-(RS)-(t-butyl)pyrrolidine

The title compound was prepared from 3-(SR)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-t-butylypyrrolidine according to procedures described in Example 3, Step 2. ^1H NMR (CDCl_3) (key peaks) δ 7.89 (m, 3H), 7.58-7.43 (m, 4H), 7.21, 7.08 (m, 2H), 7.01, 6.95 (m, 2H), 0.82, 0.99 (s, 9H); Mass Spectrum (ESI) m/e = 473 (M+1).

EXAMPLE 48

30

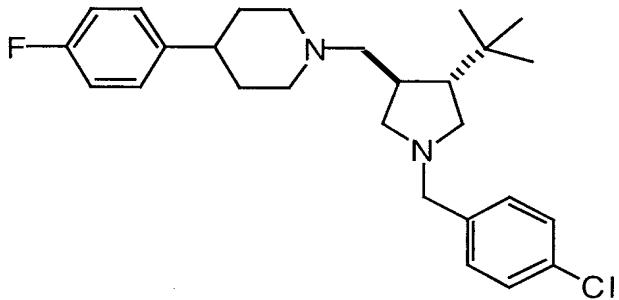


1-(3,4-Dichlorobenzoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(t-butyl)pyrrolidine

5 The title compound was prepared from 3-(SR)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-t-butylpyrrolidine according to procedures described in Example 3, Step 2. Mass Spectrum (ESI) m/e = 491 (M+1 35Cl, 35Cl) 493 (M+1 37Cl, 37Cl)

10

EXAMPLE 49



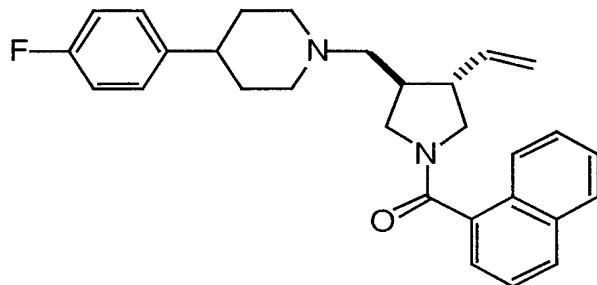
1-(4-Chlorobenzyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-(t-butyl)pyrrolidine

15 A solution of 0.025 g (0.08 mmol) of 3-(SR)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(RS)-t-butylpyrrolidine, 0.022 g (0.16 mmol) of 4-chlorobenzaldehyde and 0.043 g (0.2 mmol) of sodium triacetoxy borohydride in 5 mL of 1,2-dichloroethane was stirred for 2 h at rt. The reaction mixture was partitioned between ether and sat'd K₂CO₃ solution. The aqueous layer was extracted with ethyl acetate and the combined organic fractions were dried over Na₂SO₄, 20 filtered and the filtrate was concentrated. The residue was purified by

chromatography (silica, acetone: hexanes, 1: 3) to give the title compound. Mass Spectrum (ESI) m/e = 457 (M+1 35Cl) 459 (M+1 37Cl).

EXAMPLE 50

5

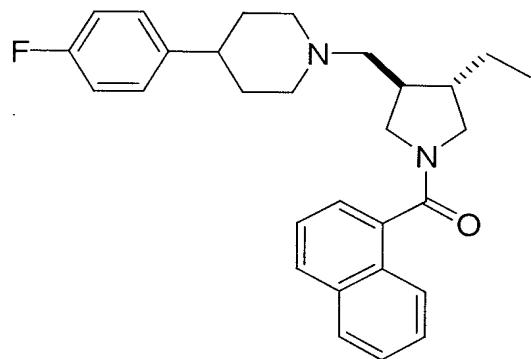


1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl-4-(SR)-(vinyl)pyrrolidine

To a suspension of 0.08 g (0.22 mmol) of methyltriphenyl phosphonium bromide ($\text{Ph}_3\text{PCH}_3\text{Br}$) in 4 mL of THF at rt was added 0.36 mL of potassium bis(trimethylsilyl)amide and the reaction mixture was stirred for 30 min. The reaction mixture was cooled to 0 °C and to it was added a solution of 0.04 g (0.089 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl-4-(SR)-formylpyrrolidine in 2 mL of THF. The reaction mixture was warmed to rt and stirred for 1.2 h. The reaction mixture was filtered through a thin pad of silica eluting with acetone: hexanes, 1: 2, then concentrated. The residue was purified by chromatography (silica, acetone: hexanes, 1: 2) to give the title compound. Mass Spectrum (ESI) m/e = 444 (M+1).

20 The following compounds are prepared as described in Examples 1, 37 or 47.

EXAMPLE 51

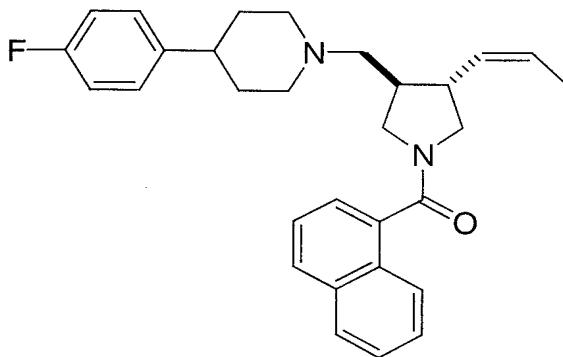


1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(ethyl)pyrrolidine

5 A mixture of 0.023 g (5 mmol) of 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine and 0.025 g of Pd/C (10%) in 8 mL of CH₃OH was hydrogenated under H₂ (50 psi) for 72 h. The reaction mixture was filtered and concentrated to give the title compound. Mass Spectrum (CI) m/e 444 (M+1).

10

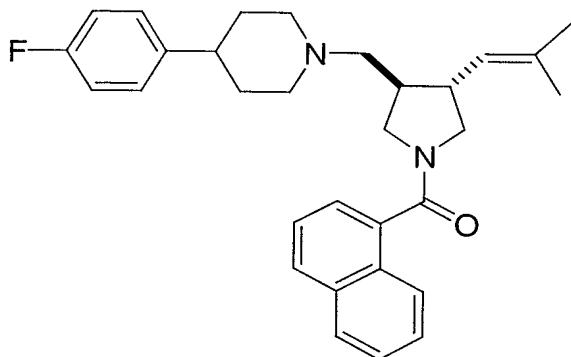
EXAMPLE 52



15 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(prop-1-enyl)pyrrolidine

The title compound was prepared according to procedures described in Example 50. Mass Spectrum (CI) m/e 457 (M+1).

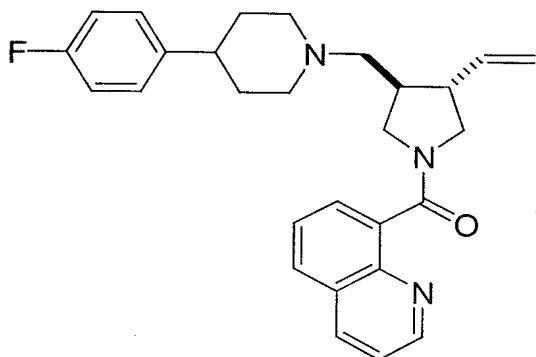
EXAMPLE 53



1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-methylprop-5
1-enyl)pyrrolidine

The title compound was prepared according to procedures described in Example 50. Mass Spectrum (CI) m/e 471 (M+1).

EXAMPLE 54



10

1-(8-Quinolincarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine

The title compound was prepared from 3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-

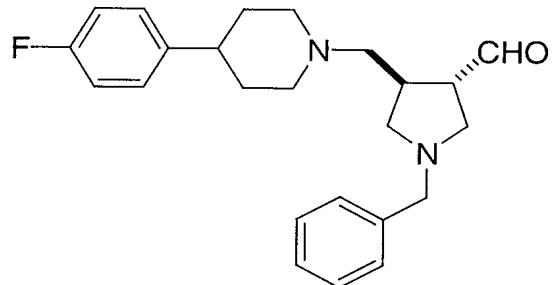
15 4-(SR)-(vinyl)pyrrolidine

and 8-quinolincarboxylic acid as described in Example 43. Mass Spectrum (CI) m/e 444 (M+1).

Preparation of 3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine

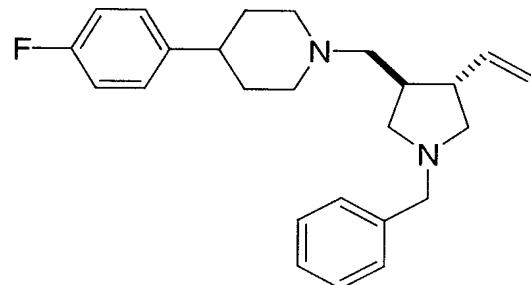
20

Step 1. 1-Benzyl-3-(RS)- (4-fluorophenyl)piperidinylmethyl)-4-(SR)-(formyl)pyrrolidine



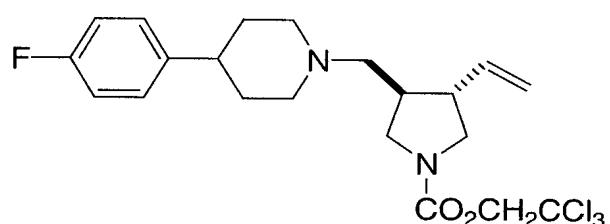
5 The title compound was prepared from 1-benzyl-3-(RS)- (4-fluorophenyl)piperidinylmethyl)-4-(SR)-(hydroxymethyl)pyrrolidine (Example 2) according to procedures described in Example 4.

10 Step 2. 1-Benzyl-3-(RS)- (4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine



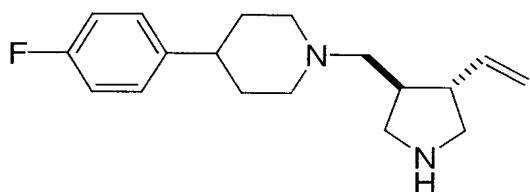
15 The title compound was prepared from 1-benzyl-3-(RS)- (4-fluorophenyl)piperidinylmethyl)-4-(SR)-(formyl)pyrrolidine according to procedures described in Example 50.

Step 3. 1-(2,2,2-Trichloroethoxycarbonyl)-3-(RS)- (4-Fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine



To a solution of 0.625 g (1.4 mmol) of 1-benzyl-3-(RS)- (4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine in 5 mL of THF at rt was added 0.21 mL (1.55 mmol) of 2,2,2-Trichloroethylchloroformate and the reaction mixture was stirred for 1 h. The reaction mixture was diluted with ether and was washed with sat'd NaHCO₃ and NaCl solutions, dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, hexanes: EtOAc, 4:1) to give 0.76 g of the title compound.

Step 4. 3-(RS)- (4-Fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine

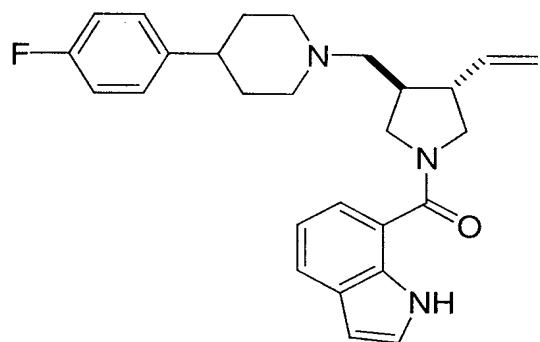


10

A mixture of 0.76 g (1.4 mmol) of 1-(2,2,2-trichloroethoxy carbonyl)-3-(RS)- (4-Fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine and 0.45 g (7 mol) of Mg in 4 mL of HOAc was heated at 40 °C for 40 min. The reaction mixture was filtered through a thin pad of Celite and the filtrate was concentrated. The residue was dissolved in ether and the solution was washed with sat'd NaHCO₃ and NaCl solutions, dried over Na₂SO₄, filtered and the filtrate was concentrated to give 0.28 g of the title compound.

20

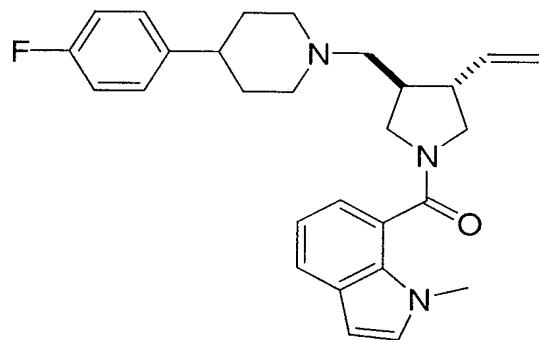
EXAMPLE 55



1-(7-Indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine

The title compound was prepared from 3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine (Example 54) and 7-indolecarboxylic acid as described in Example 43. Mass Spectrum (CI) m/e 432 (M+1).

EXAMPLE 56

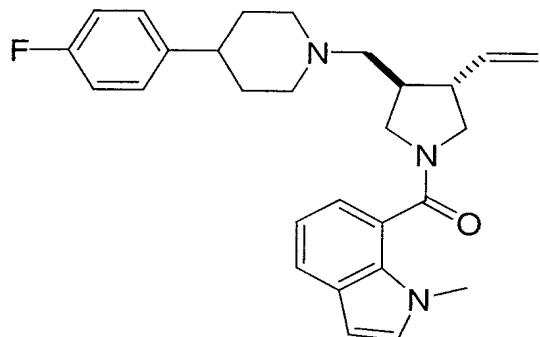


10

1-(1-Methyl-7-indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine

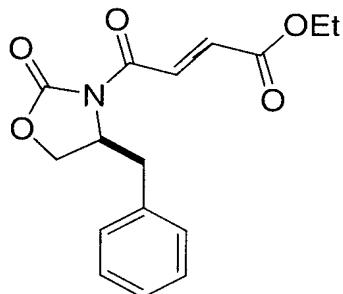
The title compound was prepared from 1-(7-indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine according to procedures described in Example 43. Mass Spectrum (CI) m/e 446 (M+1).

EXAMPLE 57



1-(1-Methyl-7-indolecarbonyl)-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(vinyl)pyrrolidine

Step 1. N-trans-3-(Ethoxycarbonyl)acryloyl-4-(S)-benzyl-2-oxazolidinone



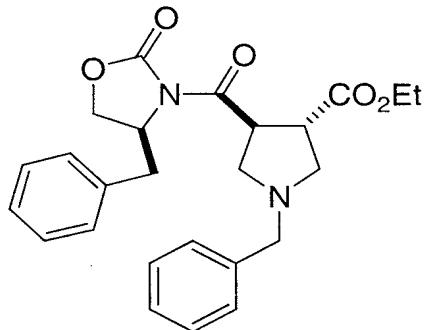
5

To a solution of 14.4 g (100 mmol) of monoethyl fumarate and 16.7 mL (120 mmol) of triethylamine in 350 mL of THF at 0 °C was added 12.7 g (105 mmol) of pivaloyl chloride. The reaction mixture was allowed to warm to rt and was stirred for 2 h, then was cooled to -78 °C.

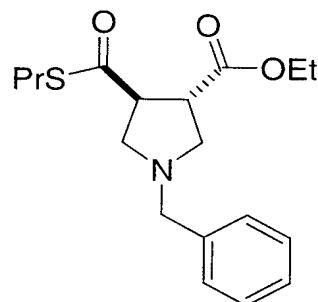
10 Meanwhile, to a solution of 18.6 g (105 mmol) of (S)-benzyl-2-oxazolidinone in 200 mL of THF at -78 °C under nitrogen, was added 75 mL of n-butyllithium (1.6M, 120 mmol) and the solution was stirred for 30 min at -78 °C. This was added via cannula to the first solution. After addition was complete, the solution was allowed to warm to room temperature for 2 h.

15 The reaction was quenched by addition of saturated aqueous NH₄Cl and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄, and filtered. The solution was concentrated followed by silica gel chromatography (25% ethyl acetate/ hexane) to afford 21.4 g the title compound; ¹H NMR (CDCl₃) δ 8.15 (d, 1H, J = 16 Hz), 6.98 (d, 1H, J = 16 Hz), 4.65 - 4.80 (m, 1H), 4.10 - 4.33 (m, 5H), 3.28 (d of d, 1H, J = 13.5, 3.2 Hz), 2.81 (d of d, 1H, J = 13.3, 9.4 Hz), 1.21 – 1.35 (m, 3H); Mass spectrum (ESI) m/e = 304 (M+1).

20 Step 2. (S)-N-[(1-Benzyl)-4-(S)-(ethoxycarbonyl)-3-(R)-pyrrolidinylcarbonyl]-4-benzyl-2-oxazolidinone and (S)-N-[(1-Benzyl)-4-(R)-(ethoxycarbonyl)-3-(S)-pyrrolidinylcarbonyl]-4-benzyl-2-oxazolidinone

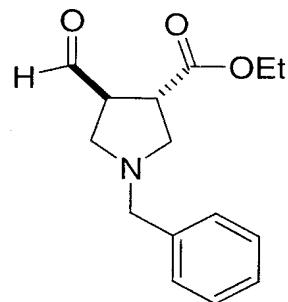


To a solution of 20 g (66 mmol) of N-trans-3-(ethoxycarbonyl) acryloyl-4-(S)-benzyl-2-oxazolidinone (Step 1) in 200 mL of CH_2Cl_2 at 0 °C was 5 added 16.6 g (70 mmol) of N-methoxymethyl-N-trimethylsilylmethylbenzylamine, and 1 mL (13.4 mmol) of trifluoroacetic acid and the solution was stirred at 0 °C for 2 h under nitrogen. The solution was poured into sat'd NaHCO_3 solution and the layers were separated. The aqueous layer was washed with CH_2Cl_2 and the combined organic fractions were washed with sat'd NaCl solution, dried over MgSO_4 , filtered, 10 and the filtrate was concentrated. The residue was purified by silica gel chromatography (ethyl acetate: hexanes, 1:4) to afford 10.1 g of the title compound (S)-N-[(1-Benzyl)-4-(S)-(ethoxycarbonyl)-3-(R)-pyrrolidinylcarbonyl]-4-benzyl-2-oxazolidinone. ^1H NMR (CDCl_3) δ 7.18-7.37 (m, 10H), 4.33 - 4.38 (m, 1H), 4.48 - 4.44 (m, 1H), 3.71 (d, 1H, J = 13.1 Hz), 3.61 (d, 1H, J = 13.1Hz), 1.26 (t, 7.1Hz); 15 Mass spectrum (ESI) m/e = 437 (M+1).
 Futher elution afforded the title compound (S)-N-[(1-Benzyl)-4-(R)-(ethoxycarbonyl)-3-(S)-pyrrolidinylcarbonyl]-4-benzyl-2-oxazolidinone; ^1H NMR (CDCl_3) δ 7.22 - 7.36 (m, 10H), 4.67 - 4.71 (m, 1H), 4.44 - 4.48 (m, 1H), 3.61 (d, 1H, J = 13.1 Hz), 3.67 (d, 1H, J = 13.1Hz), 1.28 (t, 7.1Hz); Mass spectrum (ESI) m/e = 437 (M+1).
 20 Step 3. 1-Benzyl-3-(S)-(n-propanethiocarbonyl)-4-(S)-(ethoxycarbonyl)pyrrolidine



To a cooled (-78 °C) solution of 5.7 g (75.0 mmol) of propanethiol in 250 mL THF was added 34.4 mL n-butyllithium (1.6M, 55.0 mmol) and the solution was stirred for 45 min at -78 °C under nitrogen and then warmed to -10 °C. To the 5 resulting white suspension was added a solution of 9.6 g (22.0 mmol) of (S)-N-[(1-Benzyl)-4-(R)-(ethoxycarbonyl)-3-(S)-pyrrolidinylcarbonyl]-4-benzyl-2-oxazolidinone in 250 mL THF. The reaction was stirred for 30 min and then removed from the bath and allowed to warm to rt over 1 h. The clear solution was partitioned between 1.5 L of ether and 500 mL of 1M NaOH and the layers were separated. The 10 aqueous layer was washed with ether and the combined organic fractions were washed with sat'd NCl solution, dried over MgSO₄, filtered, and the filtrate was concentrated. The residue was purified by silica gel chromatography (acetone: hexanes, 1:4) to afford 6.6 g of the title compound; Mass spectrum (ESI) m/e = 336 (M+1).

15 Step 4. 1-Benzyl-3-(S)-(formyl)-4-(S)-(ethoxycarbonyl)pyrrolidine

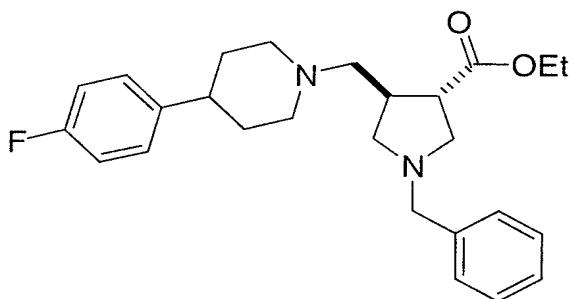


To a mixture of 0.375 g of 10% Pd/C and 6.5 g (19.4 mmol) of 1-benzyl-3-(S)-(n-propanethiocarbonyl)-4-(S)-(ethoxycarbonyl)pyrrolidine in 30 mL 20 acetone was added dropwise 7.5 mL (47.0 mmol) of triethylsilane over 15 min. The mixture was allowed to stir for 45 min after addition was complete. The reaction

mixture was filtered through a thin pad of celite and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone:hexanes, 1:4) to give 4.2 g of title compound; ^1H NMR (CDCl_3) δ 9.69 (s, 1H), 7.25 -7.33 (m, 5H), 4.18 (q, 2H, J = 7.1 Hz), 4.44 - 4.48 (m, 1H), 3.61 (d, 1H, J = 13.5 Hz), 3.64 (d, 1H, J = 13.5 Hz), 3.32 (m, 1H), 3.46 (m, 1H), 1.27 (t, 7.1 Hz); Mass spectrum (ESI) m/e = 262 (M+1).

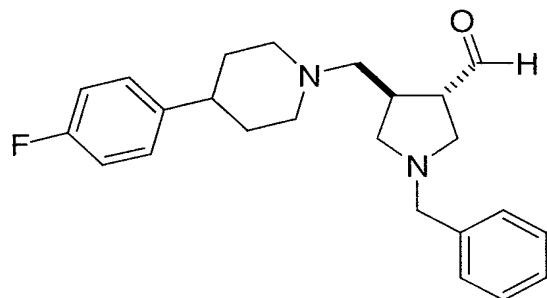
Step 5. 1-Benzyl-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(ethoxycarbonyl)pyrrolidine

10



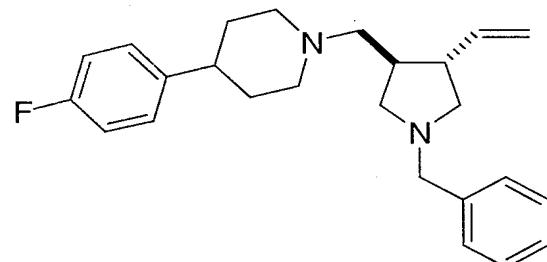
To a solution of 4.0 g (15.3 mmol) of 1-benzyl-3-(S)-(formyl)-4-(S)-(ethoxycarbonyl)pyrrolidine in 50 mL of dichloroethane at 0 °C was added 3.3 g (18.4 mmol) of 4-fluorophenyl-4-piperidine and the reaction mixture was allowed to stir for 15 min. To the reaction mixture was added 6.7g (32.0 mmol) of sodium triacetoxyborohydride and the solution was stirred for 30 min then it was warmed to rt. The reaction mixture was quenched with 15 mL saturated KHCO_3 solution, partitioned between 300 mL of ether and 10 mL of water and the layers were separated. The aqueous layer was washed with 10 mL of ethyl acetate and the combined organic fractions were washed with sat'd NaCl solution, dried over MgSO_4 , filtered, and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone: hexanes, 1:4) to afford 5.32 g of the title compound; ^1H NMR (CDCl_3) δ 7.18 -7.33 (m, 7H), 6.95 - 7.00 (m, 2H), 4.15 (q, 2H, J = 7.0 Hz), 4.44 - 4.48 (m, 1H), 3.65 (d, 1H, J = 12.6 Hz), 3.56 (d, 1H, J = 12.6 Hz), 3.40 (m, 1H), 3.03 (m, 2H), 2.45 (m, 2H), 2.07 (m, 2H), 1.6- 1.8 (m, 4H), 1.23 (t, 7.0 Hz); Mass spectrum (ESI) m/e = 425 (M+1).

Step 6. 1-Benzyl-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(formyl) pyrrolidine



5 To a cooled (-65 °C) solution of 2.1 g (50.0 mmol) of 1-benzyl-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(ethoxycarbonyl)pyrrolidine in 100 mL toluene was added 43.5 mL of diisobutylaluminum hydride (DIBAL-H) (1.5 M in toluene, 65.0 mmol) dropwise over 30 min and the solution was stirred for 2 h at - 60 -65 °C under nitrogen. The reaction was quenched with 1 mL MeOH and removed
10 from bath and allowed to stir at rt for 10 min. To the solution was added 200 mL of saturated Rochelles salt solution and 100 mL ethyl acetate and the mixture was stirred until the solution cleared. The layers were separated and the organic fraction was washed with sat'd NaCl solution, dried over MgSO₄, filtered, and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone: hexanes, 15 1:4) to afford 1.49 g of the title compound; Mass spectrum (ESI) m/e = 381 (M+1).

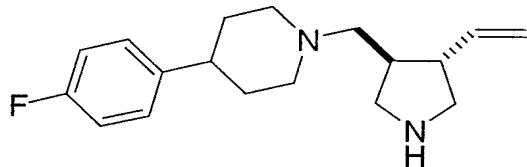
Step 7. 1-Benzyl-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(vinyl) pyrrolidine



20 To a mixture of 1.65 g (4.62 mmol) methyl triphenylphosphonium bromide in 10 mL THF at -78 °C was added 8.6 mL of potassium bis(trimethylsilyl)amide (KHMDS, 0.5M in toluene, 4.3 mmol) and the solution was

stirred for 30 min at -78 °C under nitrogen. To this mixture was added a solution of 1.25 g (3.3 mmol) of 1-benzyl-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(formyl) pyrrolidine in 5 ml THF. The reaction was warmed to rt over 2 h. The reaction was partitioned between ethyl acetate and water. The organic fraction was washed with sat'd NaCl solution, dried over MgSO₄, filtered, and the filtrate was concentrated. The residue was purified by chromatography (silica, acetone: hexanes, 1:4) to afford 0.98 g of the title compound; Mass spectrum (ESI) m/e = 379 (M+1).

Step 8. 3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(vinyl) pyrrolidine
10



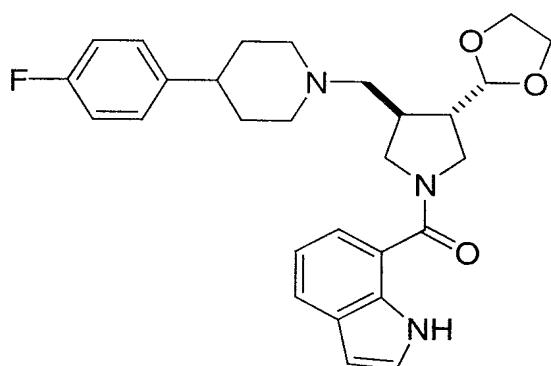
To a solution of 0.9 g (2.38 mmol) of 1-benzyl-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(vinyl) pyrrolidine in 20 mL THF at 0 °C was added 0.69 mg (2.65 mmol) of 9-fluorenylmethoxycarbonylchloride (FMOC-Cl) and the solution was stirred for 2 h. The reaction was partitioned between ethyl acetate and sat'd NaHCO₃ solution and the layers were separated. The aqueous layer was washed with ethyl acetate and the combined organic fractions were washed with sat'd NaCl solution, dried over MgSO₄, filtered, and the filtrate was concentrated. The residue was filtered through a pad of silica with 30% ethyl acetate/hexane and concentrated. The residue was dissolved in 5 mL DMF and 1 mL of diethylamine was added and the solution was stirred for 2 h at rt under nitrogen. An additional 0.5 mL diethylamine was added and allowed to stir 1 hr. The reaction was concentrated and the residue dissolved in dichloromethane and filtered through a pad of silica with 30% ethyl acetate/hexane to remove impurities and then the pad of silica was washed with CHCl₃/MeOH/NH₃(aq)(90:10:1) and concentrated to collect 0.512 g of the title compound; Mass spectrum (ESI) m/e = 289 (M+1).

Step 9. 1-(1-Methyl-7-indolecarbonyl)-3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(vinyl)pyrrolidine

The title compound was prepared from 3-(R)-4-(4-fluorophenyl)piperidinylmethyl)-4-(S)-(vinyl) pyrrolidine and 1-methylindole-7-carboxylic acid (Example 47, Step 3) according to procedures described in Example 43. The residue was purified by chromatography (HPLC Waters Nova-Pak Silica 5 25X10 RCM 25-40% acetone in hexanes) to give the title compound. ^1H NMR (CD₃OD) δ 7.66 (m, 1H), 6.98 - 7.26 (m, 7H), 6.50 (m, 1H), 5.60 - 5.88 (m, 1H), 5.18 - 5.38 (m, 2H), 4.00 - 4.34 (m, 1H), 3.80 (m, 3H), 2.55 - 3.75 (m, 12H), 1.93 - 2.09 (m, 4H); Mass spectrum (ESI) m/e = 446 (M+1). $[\alpha]_D = -38.8$ (c = 0.025, CHCl₃).

10

EXAMPLE 58

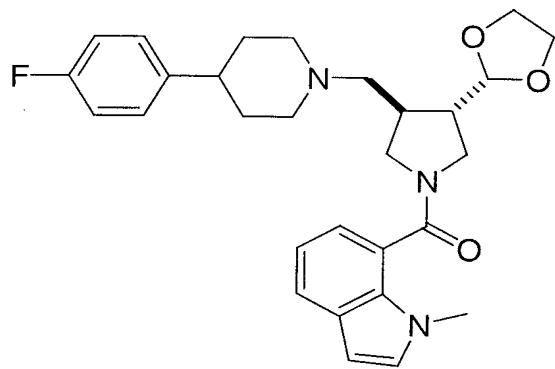


15 1-(7-Indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine

The title compound was prepared from 3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine (Example 33, Step 3) and 7-indolecarboxylic acid according to procedures described in Example 42. Mass Spectrum (CI) m/e 478 (M+1).

20

EXAMPLE 59

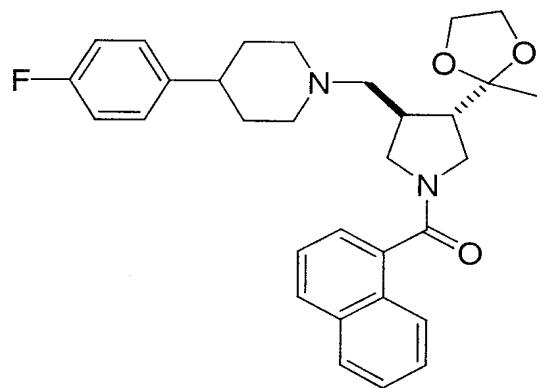


1-(1-Methyl-7-indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine

5 The title compound was prepared from 1-(7-indolecarbonyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine according to procedures described in Example 43. Mass Spectrum (CI) m/e 492 (M+1).

10

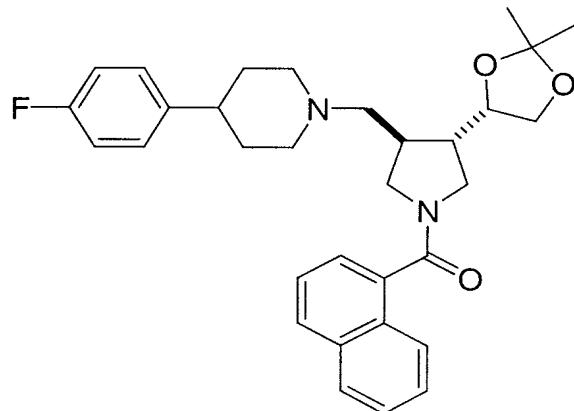
EXAMPLE 60



1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-methyl-1,3-dioxolan-2-yl)pyrrolidine

15 The title compound was prepared from 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(acetyl)pyrrolidine (Example 27) according to procedures described in Example 33. Mass Spectrum (CI) m/e 503 (M+1).

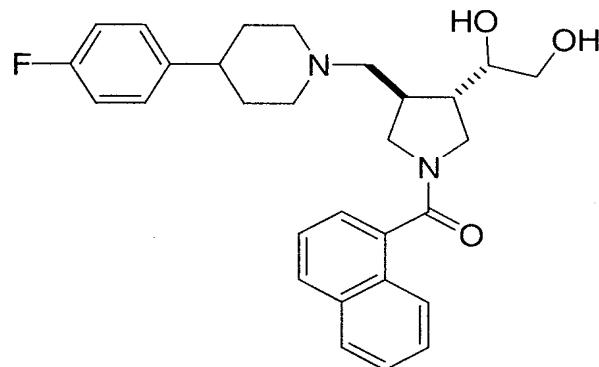
EXAMPLE 61



5

1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2,2-dimethyl-1,3-dioxolan-5-yl)pyrrolidine

10 Step 1. 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,2-dihydroxyethyl)pyrrolidine



15 To a solution of 0.023 g (0.05 mmol) of 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(vinyl)pyrrolidine (Example 50) in 1 mL of pyridine, 2 mL of THF and 1 mL of H₂O at rt was added 0.016 g (0.06 mmol) of OsO₄, and the reaction was stirred for 2 h. The reaction mixture was diluted with THF and H₂S gas was bubbled through it for 5 min. The reaction mixture was filtered through a thin pad of celite and the filtrate was concentrated. The residue was

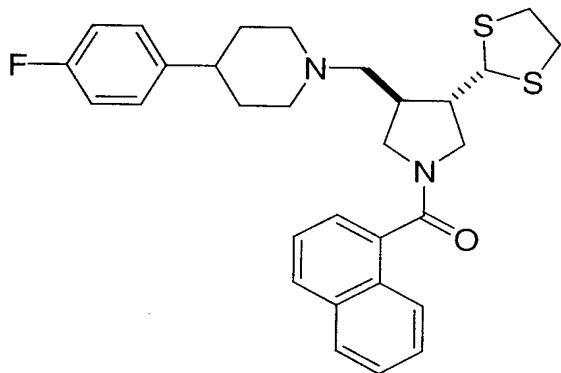
purified by chromatography (silica, CH_2Cl_2 : NH_3 (2N in CH_3OH), 95: 5) to give 0.013 g of the title compound.

Step 2. 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2,2-dimethyl-1,3-dioxolan-5-yl)pyrrolidine

A solution of 0.013 g (0.027 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,2-dihydroxyethyl)pyrrolidine, 0.2 mL (1.6 mmol) of 2,2-dimethoxypropane and 0.01 g of p-toluenesulfonic acid in 2 mL of DMF was stirred at rt for 16 h. The reaction mixture was concentrated and the residue was dissolved in ether. The ether solution was washed with sat'd NaHCO_3 and sat'd NaCl solutions, dried over MgSO_4 , filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, hexanes, EtOAc : NH_3 (2N in CH_3OH), 10: 10: 1) to give the two isomers of the title compound.

Isomer #1 Mass Spectrum (CI) m/e 517 (M+1). Isomer #2 Mass Spectrum (CI) m/e 15 517 (M+1).

EXAMPLE 62



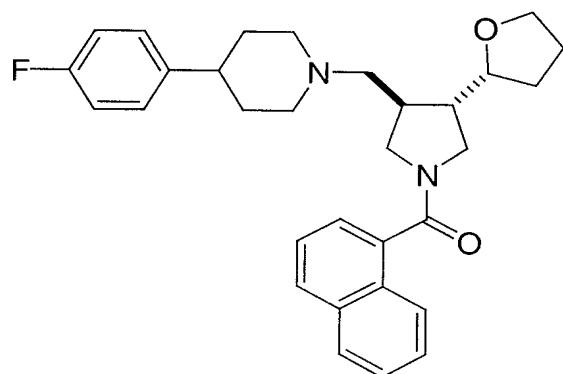
20 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dithiolan-2-yl)pyrrolidine

A solution of 0.11 g (0.254 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(formyl)pyrrolidine, 0.043 mL (0.5 mmol) of 1,2-ethanedithiol and 0.042 mL (0.3 mmol) of $\text{BF}_3 \cdot 2\text{HOAc}$ in 4 mL of CH_2Cl_2 was stirred at rt for 2 h. The reaction mixture was diluted with ether and was washed with sat'd NaHCO_3 and NaCl solutions, dried over Na_2SO_4 , filtered and the filtrate was

concentrated. The residue was purified by chromatography (silica, hexanes: EtOAc: NH₃ (2N in CH₃OH), 20: 20: 1) to give the title compound. Mass Spectrum (CI) m/e 521 (M+1).

5

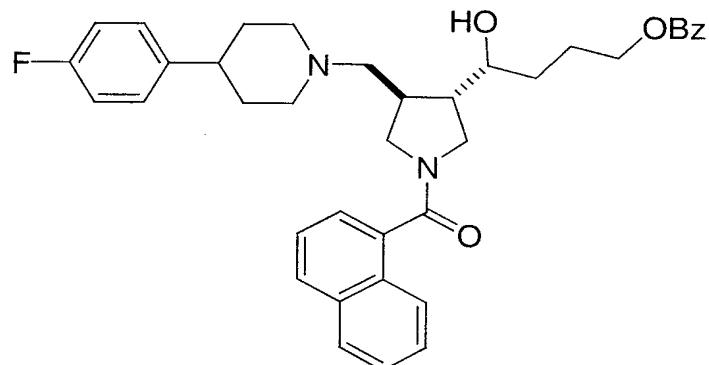
EXAMPLE 63



1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-
10 (tetrahydrofuran-2-yl)pyrrolidine

10

Step 1. 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-benzyloxy-1-hydroxy-n-but-1-yl)pyrrolidine

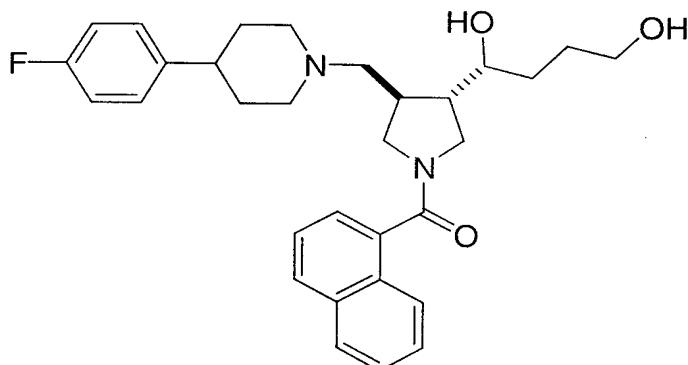


15

A mixture of 1 mL (5.67 mmol) of 3-benzyloxy-1-bromopropane and 0.19 g (7.9 mmol) of Mg in 4 mL of THF was stirred at 65 °C for 1 h. To this stirred reaction mixture was added a solution of 0.166 g (0.37 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(formyl)pyrrolidine in 2 mL of

THF and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with ether and was washed with sat'd NaHCO₃ and NaCl solutions, dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, hexanes: EtOAc: NH₃ (2N in CH₃OH) 10: 10: 1) to give 0.16 g of the title compound.

5 Step 2. 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,4dihydroxy-n-but-1-yl)pyrrolidine



10

A mixture 0.1 g (0.17 mmol) of -(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-benzyloxy-1-hydroxy-n-but-1-yl)pyrrolidine and 0.12 g of Pd/C (10%) in 8 mL of a 4.4% solution of HCO₂H in CH₃OH was heated at reflux for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in CH₂Cl₂ and was washed with sat'd NaHCO₃ solution, dried over Na₂SO₄, filtered and the filtrate was concentrated. The title compound was used without further purification.

15 Step 3. 1-(1-Naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(tetrahydrofuran-2-yl)pyrrolidine

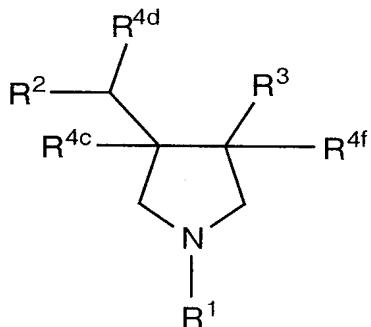
20 A solution of 0.018 g (0.036 mmol) of 1-(1-naphthoyl)-3-(RS)-4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,4dihydroxy-n-but-1-yl)pyrrolidine and 0.021 g (0.11 mmol) of p-toluenesulfonic acid in 4 mL of benzene was heated at reflux for 2 h. The reaction mixture was diluted with ether and was washed with sat'd NaHCO₃ and NaCl solutions, dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, hexanes: EtOAc:

NH₃ (2N in CH₃OH) 10: 10: 1) to give the title compound. Mass Spectrum (CI) m/e 487 (M+1).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



5

I

wherein:

R¹ is -X-R⁸, wherein X is selected from the group consisting of:

- (1) -CH₂-,
- (2) -CO-,
- 10 (3) -CH₂CH₂-,
- (4) -CH₂CH₂CH₂-, and
- (5) -CH(C₁₋₆ alkyl)-,

and wherein R⁸ is selected from:

15 phenyl, naphthyl, biphenyl, fluorenyl, indenyl, indanyl, dihydronaphthyl, tetrahydronaphthyl, octahydronaphthyl, adamantyl, and heterocycle, which may be unsubstituted or substituted, where the substituents are independently selected from:

20 (a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

(i) hydroxy,
 (ii) halogen,
 (iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

5 (A) phenyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

10 (B) naphthyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

15 (C) heterocycle,unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,

20 (D) hydroxy,
(E) -O(C₁-6 alkyl),
(F) -CO₂(C₁-6 alkyl),
(G) -S(O)_n-(C₁-6 alkyl), wherein n is an
integer selected from 0, 1 and 2,

25 (H) halogen,
(I) -NH₂,
(J) -NH(C₁-6 alkyl), and
(K) -N(C₁-6 alkyl)(C₁-6 alkyl),

30 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,

35

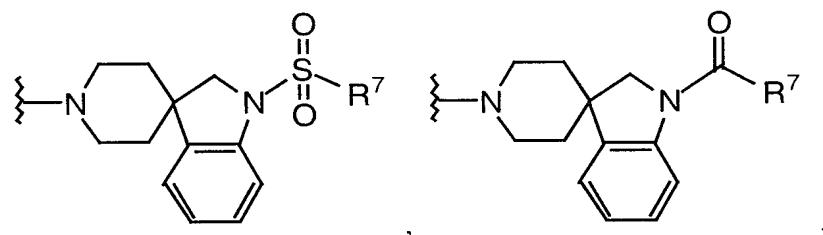
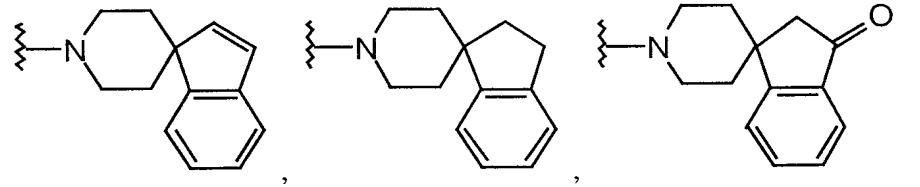
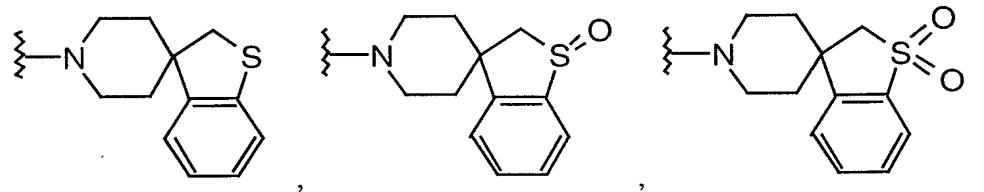
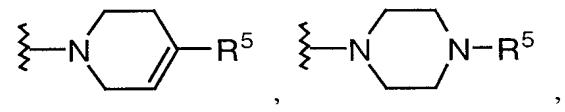
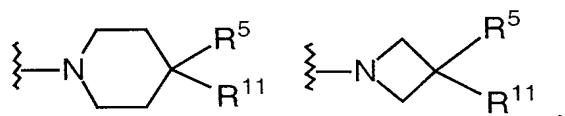
(ix) -S(O)₂-NR⁹R¹⁰, wherein n is an integer selected from
0, 1 and 2,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
5 (xii) -S(O)_n-R⁹,
(xiii) -CF₃,
(xiv) -CHF₂,
(xv) -CH₂F,
(xvi) -O-R⁹,
10 (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
(xviii) phenyl,
(xix) naphthyl,
(xx) indenyl,
(xxi) indanyl,
15 (xxii) heterocycle,
(xxiii) -CO-phenyl,
(xxiv) -CO-naphthyl,
(xxv) -CO-indenyl,
(xxvi) -CO-indanyl,
20 (xxvii) -CO-heterocycle,
(xxviii) -OCO-R⁹,
(xxix) -OCO₂-R⁹, and
(xxx) -CO-R⁹,
(b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the
25 alkyl, alkenyl, or alkynyl is unsubstituted or substituted,
wherein the substituents are independently selected from:
(i) hydroxy,
(ii) halogen,
(iii) -NR⁹R¹⁰,
30 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
(viii) -NR⁹CO-NR⁹R¹⁰,

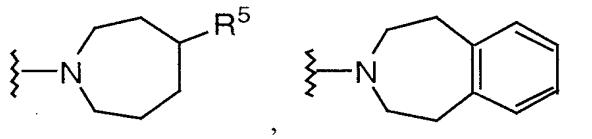
- (ix) -S(O)₂-NR⁹R¹⁰,
- (x) -NR⁹S(O)₂-R¹⁰,
- (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
- (xii) -S(O)_n-R⁹,
- 5 (xiii) -CF₃,
- (xiv) -CHF₂,
- (xv) -CH₂F,
- (xvii) -O-R⁹,
- (xviii) -O(C₁₋₆ alkyl)-O-R⁹,
- 10 (xix) phenyl,
- (xx) naphthyl,
- (xxi) indenyl,
- (xxii) indanyl,
- (xxiii) heterocycle,
- 15 (xxiv) -CO-phenyl,
- (xxv) -CO-naphthyl,
- (xxvi) -CO-indenyl,
- (xxvii) -CO-indanyl,
- (xxviii) -CO-heterocycle,
- 20 (xxix) -OCO-R⁹,
- (xxx) -OCO₂-R⁹, and
- (c) -CO-R⁹,
- (d) hydroxy,
- 25 (e) halogen,
- (f) -NR⁹R¹⁰,
- (g) -NR⁹-COR¹⁰,
- (h) -NR⁹-CO₂R¹⁰,
- (i) -CO-NR⁹R¹⁰,
- 30 (j) -OCO-NR⁹R¹⁰,
- (k) -NR⁹CO-NR⁹R¹⁰,
- (l) -S(O)₂-NR⁹R¹⁰,
- (m) -NR⁹S(O)₂-R¹⁰,
- (n) -NR⁹S(O)₂-NR⁹R¹⁰,

- (o) $-\text{S}(\text{O})_n\text{R}^9$,
- (p) $-\text{CF}_3$,
- (q) $-\text{CHF}_2$,
- 5 (r) $-\text{CH}_2\text{F}$,
- (s) $-\text{OCO-R}^9$,
- (t) $-\text{OCO}_2\text{R}^9$, and
- (u) $-\text{CO-R}^9$;

R^2 is selected from the group consisting of:

10





wherein R⁵ is a selected from:

- (1) -NR⁶CO-O-R⁷, wherein R⁶ is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkyl-C₅₋₆ cycloalkyl, and R⁷ is C₁₋₆ alkyl, C₅₋₆ cycloalkyl, benzyl or phenyl, wherein the alkyl, cycloalkyl, benzyl or phenyl is unsubstituted or substituted with halogen, C₁₋₃alkyl, C₁₋₃alkoxy or trifluoromethyl,
- (2) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,
- (3) -pyridyl,
- (4) -thienyl,
- (5) -C₁₋₆alkyl-phenyl, -C₁₋₆alkyl-naphthyl, -C₁₋₆alkyl-indenyl, -C₁₋₆alkyl-indanyl, and -C₁₋₆alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl; and wherein the -C₁₋₆alkyl is optionally substituted with oxo, hydroxy, C₁₋₆alkoxy, acetoxy, or halogen,
- (6) -O-C₁₋₆alkyl-phenyl, -O-C₁₋₆alkyl-naphthyl, -O-C₁₋₆alkyl-indenyl, -O-C₁₋₆alkyl-indanyl, and -O-C₁₋₆alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl,
- (7) -C₁₋₄alkyl-O-C₁₋₄alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl, and
- (8) -C₁₋₄alkyl-S(O)_n-C₁₋₄alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl,

C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl;

and wherein R¹¹ is selected from:

5 (1) -hydrogen,
(2) -OH,
(3) -C₁-6alkyl, and
(4) -halogen;

R³ is selected from the group consisting of:

10 (1) -CHO,
(2) -CO₂(C₁-6 alkyl),
(3) -CO-R⁹,
(4) -CONR⁹R¹⁰,
(5) -CONR⁹-COR¹⁰,
15 (6) -CONR⁹-CO₂R¹⁰,
(7) -C(R⁹)(OR⁹)(OR¹⁰),
(8) -C(R⁹)(SR⁹)(SR¹⁰),
(9) -C(R⁹)(OR¹⁴)(OR¹⁵), wherein R¹⁴ and R¹⁵ are joined together in a
20 C₂-3 alkyl group to form a 5- or 6-membered ring which is substituted
with R¹² and R¹³ wherein:

R¹² and R¹³ are independently selected from:

25 (a) hydrogen,
(b) -CO₂(C₁-6 alkyl),
(c) hydroxy,
(d) halogen,
(e) -NR⁹R¹⁰,
(f) -NR⁹-COR¹⁰,
(g) -NR⁹-CO₂R¹⁰,
(h) -CF₃,
30 (i) -CHF₂,
(j) -CH₂F,
(k) -O-R⁹,

(l) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

5 (i) -CO₂(C₁-6 alkyl),
(ii) hydroxy,
(iii) halogen,
(iv) -NR⁹R¹⁰,
(v) -NR⁹-COR¹⁰,
(vi) -NR⁹-CO₂R¹⁰,

10 (vii) phenyl,
(viii) -CF₃,
(ix) -CHF₂,
(x) -CH₂F, and
(xi) -O-R⁹,

15 (p) phenyl or heterocycle, wherein the phenyl or heterocycle is unsubstituted or substituted, wherein the substituents are independently selected from:
(i) -CO₂(C₁-6 alkyl),
(ii) hydroxy,
20 (iii) halogen,
(iv) -NR⁹R¹⁰,
(v) -NR⁹-COR¹⁰,
(vi) -NR⁹-CO₂R¹⁰,
(vii) phenyl,
25 (viii) -CF₃,
(ix) -CHF₂,
(x) -CH₂F, and
(xi) -O-R⁹,

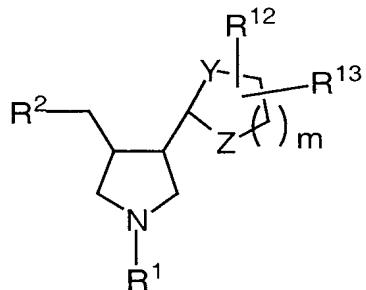
(11) -C(R⁹)(SR¹⁴)(SR¹⁵),
30 (12) -cyclopentyl, which is substituted with R¹² and R¹³,
(13) -cyclohexyl, which is substituted with R¹² and R¹³,
(14) -tetrahydrofuranyl, which is substituted with R¹² and R¹³,
(15) -tetrahydropyranyl, which is substituted with R¹² and R¹³;

R^{4c} , R^{4d} , and R^{4f} are independently selected from the group consisting of:

- (1) hydrogen, and
- (2) C₁₋₆ alkyl;

5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. A compound of the formula Ib:



Ib

10 wherein:

R^1 is $-X-R^8$, wherein X is selected from the group consisting of:

- (1) -CH₂-,
- (2) -CO-, and
- (3) -CH₂CH₂-,

15 and wherein R^8 is selected from:

phenyl, naphthyl, biphenyl, fluorenyl, indenyl, indanyl, dihydronaphthyl, tetrahydronaphthyl, octahydronaphthyl, adamantyl, and heterocycle, which may be unsubstituted or substituted, where the substituents are independently selected from:

- (a) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:
 - (i) hydroxy,
 - (ii) halogen,
 - (iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is

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unsubstituted or substituted, wherein the substituents are independently selected from:

(A) phenyl, unsubstituted or substituted, wherein the substituents are independently selected from: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl), -N(C₁-6 alkyl)(C₁-6 alkyl), or trifluoromethyl,

(B) naphthyl, unsubstituted or substituted, wherein the substituents are independently selected from: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl), -N(C₁-6 alkyl)(C₁-6 alkyl), or trifluoromethyl,

(C) heterocycle,unsubstituted or substituted, wherein the substituents are independently selected from: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl), -N(C₁-6 alkyl)(C₁-6 alkyl), or trifluoromethyl,

(D) hydroxy,

(E) -O(C₁-6 alkyl),

(F) -CO₂(C₁-6 alkyl),

(G) -S(O)_n-(C₁-6 alkyl), wherein n is an integer selected from 0, 1 and 2,

(H) halogen,

(I) -NH₂,

(J) -NH(C₁-6 alkyl), and

(K) -N(C₁-6 alkyl)(C₁-6 alkyl),

(iv) -NR⁹-COR¹⁰,

(v) -NR⁹-CO₂R¹⁰,

(vi) -CO-NR⁹R¹⁰,

- (vii) -OCO-NR⁹R¹⁰,
- (viii) -NR⁹CO-NR⁹R¹⁰,
- (ix) -S(O)₂-NR⁹R¹⁰, wherein n is an integer selected from
5 0, 1 and 2,
- (x) -NR⁹S(O)₂-R¹⁰,
- (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
- (xii) -S(O)_n-R⁹,
- (xiii) -CF₃,
- (xiv) -CHF₂,
- 10 (xv) -CH₂F,
- (xvi) -O-R⁹,
- (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
- (xviii) phenyl,
- (xix) naphthyl,
- 15 (xx) indenyl,
- (xxi) indanyl,
- (xxii) heterocycle,
- (xxiii) -CO-phenyl,
- (xxiv) -CO-naphthyl,
- 20 (xxv) -CO-indenyl,
- (xxvi) -CO-indanyl,
- (xxvii) -CO-heterocycle,
- (xxviii) -OCO-R⁹,
- (xxix) -OCO₂-R⁹, and
- 25 (xxx) -CO-R⁹,

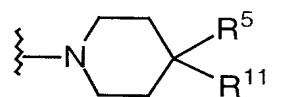
(b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:

- 30 (i) hydroxy,
- (ii) halogen,
- (iii) -NR⁹R¹⁰,
- (iv) -NR⁹-COR¹⁰,
- (v) -NR⁹-CO₂R¹⁰,
- (vi) -CO-NR⁹R¹⁰,

- (vii) -OCO-NR⁹R¹⁰,
- (viii) -NR⁹CO-NR⁹R¹⁰,
- (ix) -S(O)₂-NR⁹R¹⁰,
- (x) -NR⁹S(O)₂-R¹⁰,
- 5 (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
- (xii) -S(O)_n-R⁹,
- (xiii) -CF₃,
- (xiv) -CHF₂,
- (xv) -CH₂F,
- 10 (xvii) -O-R⁹,
- (xviii) -O(C₁₋₆ alkyl)-O-R⁹,
- (xix) phenyl,
- (xx) naphthyl,
- (xxi) indenyl,
- 15 (xxii) indanyl,
- (xxiii) heterocycle,
- (xxiv) -CO-phenyl,
- (xxv) -CO-naphthyl,
- (xxvi) -CO-indenyl,
- 20 (xxvii) -CO-indanyl,
- (xxviii) -CO-heterocycle,
- (xxix) -OCO-R⁹,
- (xxx) -OCO₂-R⁹, and
- (c) -CO-R⁹,
- 25 (d) -NO₂,
- (e) hydroxy,
- (f) halogen,
- (g) -NR⁹R¹⁰,
- (h) -NR⁹-COR¹⁰,
- 30 (i) -NR⁹-CO₂R¹⁰,
- (j) -CO-NR⁹R¹⁰,
- (k) -OCO-NR⁹R¹⁰,
- (l) -S(O)₂-NR⁹R¹⁰,

- (m) $-\text{NR}^9\text{S(O)}_2\text{R}^{10}$,
- (n) $-\text{NR}^9\text{S(O)}_2\text{NR}^9\text{R}^{10}$,
- (o) $-\text{S(O)}_n\text{R}^9$,
- (p) $-\text{CF}_3$,
- 5 (q) $-\text{CHF}_2$,
- (r) $-\text{CH}_2\text{F}$,
- (s) $-\text{OCO-R}^9$,
- (t) $-\text{OCO}_2\text{R}^9$, and
- (u) $-\text{CO-R}^9$;

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 R^2 is:wherein R^5 is a selected from:

- (1) $-\text{NR}^6\text{CO-O-R}^7$, wherein R^6 is hydrogen, C₁₋₆ alkyl or C₁₋₆ alkyl-C₅₋₆ cycloalkyl, and R^7 is C₁₋₆ alkyl, C₅₋₆ cycloalkyl, benzyl or phenyl, wherein the alkyl, cycloalkyl, benzyl or phenyl is unsubstituted or substituted with halogen, C₁₋₃alkyl, C₁₋₃alkoxy or trifluoromethyl,
- 15 (2) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, $-\text{CO}_2(\text{C1-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl,
- (3) -pyridyl,
- (4) -thienyl,
- (5) -C₁₋₆alkyl-phenyl, -C₁₋₆alkyl-naphthyl, -C₁₋₆alkyl-indenyl, -C₁₋₆alkyl-indanyl, and -C₁₋₆alkyl-heterocycle,
- 20 25 wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, $-\text{CO}_2(\text{C1-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl;
- 30 and wherein the -C₁₋₆alkyl is optionally substituted with oxo, hydroxy, C₁₋₆alkoxy, acetoxy, or halogen,

(6) -O-C₁₋₆alkyl-phenyl, -O-C₁₋₆alkyl-naphthyl,
-O-C₁₋₆alkyl-indenyl, -O-C₁₋₆alkyl-indanyl, and
-O-C₁₋₆alkyl-heterocycle, wherein the phenyl, naphthyl, indenyl,
indanyl, or heterocycle is unsubstituted or substituted with: halogen,
hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹,
-NR⁹R¹⁰, or trifluoromethyl,
(7) -C₁₋₄alkyl-O-C₁₋₄alkyl-phenyl, wherein the phenyl is unsubstituted or
substituted with halogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy,
-CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or trifluoromethyl, and
10 (8) -C₁₋₄alkyl-S(O)_n-C₁₋₄alkyl-phenyl, wherein the phenyl is
unsubstituted or substituted with halogen, hydroxy, C₁₋₆alkyl,
C₁₋₆alkoxy, -CO₂(C₁₋₆ alkyl), -NH₂, -NHR⁹, -NR⁹R¹⁰, or
trifluoromethyl;
and wherein R¹¹ is a selected from:
15 (1) -hydrogen,
(2) -OH,
(3) -C₁₋₆alkyl, and
(4) -halogen;
20 R¹² and R¹³ are independently selected from:
(1) hydrogen,
(2) -CO₂(C₁₋₆ alkyl),
(3) hydroxy,
(4) halogen,
25 (5) -NR⁹R¹⁰,
(6) -NR⁹-COR¹⁰,
(7) -NR⁹-CO₂R¹⁰,
(8) -CF₃,
(9) -CHF₂,
30 (10) -CH₂F,
(11) -O-R⁹,
(12) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or
alkynyl is unsubstituted or substituted, wherein the substituents are
independently selected from:

- (a) $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$,
- (b) hydroxy,
- (c) halogen,
- (d) $-\text{NR}^9\text{R}^{10}$,
- 5 (e) $-\text{NR}^9\text{-COR}^{10}$,
- (f) $-\text{NR}^9\text{-CO}_2\text{R}^{10}$,
- (g) phenyl,
- (h) $-\text{CF}_3$,
- (i) $-\text{CHF}_2$,
- 10 (j) $-\text{CH}_2\text{F}$, and
- (k) $-\text{O-R}^9$,

(14) phenyl or heterocycle, wherein the phenyl or heterocycle is unsubstituted or substituted, wherein the substituents are independently selected from:

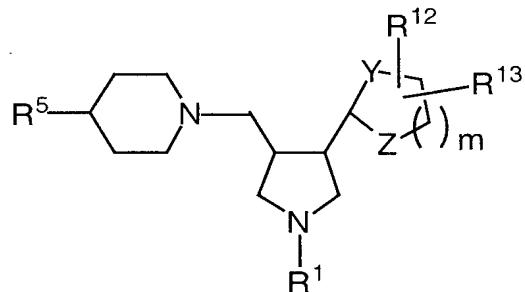
- (a) $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$,
- (b) hydroxy,
- (c) halogen,
- (d) $-\text{NR}^9\text{R}^{10}$,
- (e) $-\text{NR}^9\text{-COR}^{10}$,
- 15 (f) $-\text{NR}^9\text{-CO}_2\text{R}^{10}$,
- (g) phenyl,
- (h) $-\text{CF}_3$,
- (i) $-\text{CHF}_2$,
- (j) $-\text{CH}_2\text{F}$, and
- 20 (k) $-\text{O-R}^9$,

Y and Z are independently selected from: C_1 alkyl, $-\text{O-}$, $-\text{S(O)}_n-$ and $-\text{N}(\text{R}^9)-$;

30 m is an integer selected from 1 and 2;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. The compound of Claim 2 of the formula Id:



Id

wherein:

5 R¹ is -X-R⁸, wherein X is selected from the group consisting of:

- (1) -CH₂-, and
- (2) -CO-,

and wherein R⁸ is selected from:

10 phenyl, naphthyl, indenyl, indanyl, indolyl, quinolyl, isoquinolyl, benzofuranyl, dihydrobenzofuranyl, methylenedioxybenzoyl, benzopyrazolyl, and benzotriazolyl, which may be unsubstituted or substituted, where the substituents are independently selected from:

15 (a) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:

- (i) hydroxy,
- (ii) halogen,
- (iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from hydrogen, C₁-6 alkyl, C₂-6 alkenyl, and C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, where the substituents are independently selected from:
 - (A) phenyl, unsubstituted or substituted, where the substituents are independently selected from: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, -CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl), -N(C₁-6 alkyl)(C₁-6 alkyl), or

5 trifluoromethyl,
(B) naphthyl, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,
(C) heterocycle, unsubstituted or substituted,
wherein the substituents are
independently selected from: halogen,
hydroxy, C₁-6alkyl, C₁-6alkoxy,
-CO₂(C₁-6 alkyl), -NH₂, -NH(C₁-6 alkyl),
-N(C₁-6 alkyl)(C₁-6 alkyl), or
trifluoromethyl,
10 (D) hydroxy,
(E) -O(C₁-6 alkyl),
(F) -CO₂(C₁-6 alkyl),
(G) -S(O)_n-(C₁-6 alkyl), wherein n is an
integer selected from 0, 1 and 2,
15 (H) halogen,
(I) -NH₂,
(J) -NH(C₁-6 alkyl), and
(K) -N(C₁-6 alkyl)(C₁-6 alkyl),
20 (iv) -NR⁹-COR¹⁰,
(v) -NR⁹-CO₂R¹⁰,
(vi) -CO-NR⁹R¹⁰,
(vii) -OCO-NR⁹R¹⁰,
25 (viii) -NR⁹CO-NR⁹R¹⁰,
(ix) -S(O)_n-NR⁹R¹⁰, wherein n is an integer selected from
0, 1 and 2,
(x) -NR⁹S(O)₂-R¹⁰,
(xi) -NR⁹S(O)₂-NR⁹R¹⁰,
30 (xii) -S(O)_n-R⁹,
(xiii) -CF₃,
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- (xiv) -CHF₂,
- (xv) -CH₂F,
- (xvi) -O-R⁹,
- (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
- 5 (xviii) phenyl,
- (xix) naphthyl,
- (xx) indenyl,
- (xxi) indanyl,
- (xxii) heterocycle,
- 10 (xxiii) -CO-phenyl,
- (xxiv) -CO-naphthyl,
- (xxv) -CO-indenyl,
- (xxvi) -CO-indanyl,
- (xxvii) -CO-heterocycle,
- 15 (xxviii) -OCO-R⁹,
- (xxix) -OCO₂-R⁹, and
- (xxx) -CO-R⁹,
- (b) -O-C₁₋₆alkyl, -O-C₂₋₆ alkenyl, -O-C₂₋₆ alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:
- 20 (i) hydroxy,
- (ii) halogen,
- (iii) -NR⁹R¹⁰,
- (iv) -NR⁹-COR¹⁰,
- 25 (v) -NR⁹-CO₂R¹⁰,
- (vi) -CO-NR⁹R¹⁰,
- (vii) -OCO-NR⁹R¹⁰,
- (viii) -NR⁹CO-NR⁹R¹⁰,
- 30 (ix) -S(O)₂-NR⁹R¹⁰,
- (x) -NR⁹S(O)₂-R¹⁰,
- (xi) -NR⁹S(O)₂-NR⁹R¹⁰,
- (xii) -S(O)_n-R⁹,
- (xiii) -CF₃,
- (xiv) -CHF₂,

- (xv) -CH₂F,
- (xvii) -O-R⁹,
- (xvii) -O(C₁₋₆ alkyl)-O-R⁹,
- (xviii) phenyl,
- 5 (xix) naphthyl,
- (xx) indenyl,
- (xxi) indanyl,
- (xxii) heterocycle,
- (xxiii) -CO-phenyl,
- 10 (xxiv) -CO-naphthyl,
- (xxv) -CO-indenyl,
- (xxvi) -CO-indanyl,
- (xxvii) -CO-heterocycle,
- (xxviii) -OCO-R⁹,
- 15 (xxix) -OCO₂-R⁹, and
- (xxx) -CO-R⁹,
- (c) -NO₂,
- (d) hydroxy,
- (e) halogen,
- 20 (f) -NR⁹R¹⁰,
- (g) -NR⁹-COR¹⁰,
- (h) -NR⁹-CO₂R¹⁰,
- (i) -CO-NR⁹R¹⁰,
- (j) -OCO-NR⁹R¹⁰,
- 25 (k) -NR⁹CO-NR⁹R¹⁰,
- (l) -S(O)₂-NR⁹R¹⁰,
- (m) -NR⁹S(O)₂-R¹⁰,
- (n) -NR⁹S(O)₂-NR⁹R¹⁰,
- (o) -S(O)_n-R⁹,
- 30 (p) -CF₃,
- (q) -CHF₂,
- (r) -CH₂F,
- (s) -OCO-R⁹,
- (t) -OCO₂-R⁹, and

(u) $-\text{CO-R}^9;$

wherein R^5 is a selected from:

- 5 (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkoxy}$, $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl,
- (2) $-\text{C}_1\text{-6alkyl-phenyl}$, $-\text{C}_1\text{-6alkyl-naphthyl}$, $-\text{C}_1\text{-6alkyl-indenyl}$, $-\text{C}_1\text{-6alkyl-indanyl}$, and $-\text{C}_1\text{-6alkyl-heterocycle}$, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkoxy}$, $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl;
- 10 (3) and wherein the $-\text{C}_1\text{-6alkyl}$ is optionally substituted with oxo, hydroxy, $\text{C}_1\text{-6alkoxy}$, acetoxy, or halogen,
- 15 (4) $-\text{O-C}_1\text{-6alkyl-phenyl}$, $-\text{O-C}_1\text{-6alkyl-naphthyl}$, $-\text{O-C}_1\text{-6alkyl-indenyl}$, $-\text{O-C}_1\text{-6alkyl-indanyl}$, and $-\text{O-C}_1\text{-6alkyl-heterocycle}$, wherein the phenyl, naphthyl, indenyl, indanyl, or heterocycle is unsubstituted or substituted with: halogen, hydroxy, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkoxy}$, $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl,
- 20 (5) $-\text{C}_1\text{-4alkyl-O-C}_1\text{-4alkyl-phenyl}$, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkoxy}$, $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl, and
- 25 (6) $-\text{C}_1\text{-4alkyl-S(O)}_n\text{-C}_1\text{-4alkyl-phenyl}$, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, $\text{C}_1\text{-6alkyl}$, $\text{C}_1\text{-6alkoxy}$, $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$, $-\text{NH}_2$, $-\text{NHR}^9$, $-\text{NR}^9\text{R}^{10}$, or trifluoromethyl;

R^{12} and R^{13} are independently selected from:

- 30 (1) hydrogen,
- (2) $-\text{CO}_2(\text{C}_1\text{-6 alkyl})$,
- (3) hydroxy,
- (4) halogen,
- (5) $-\text{NR}^9\text{R}^{10}$,

- (6) -NR⁹-COR¹⁰,
- (7) -NR⁹-CO₂R¹⁰,
- (8) -CF₃,
- (9) -CHF₂,
- 5 (10) -CH₂F,
- (11) -O-R⁹,
- (12) C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is unsubstituted or substituted, wherein the substituents are independently selected from:
- 10 (a) -CO₂(C₁-6 alkyl),
- (b) hydroxy,
- (c) halogen,
- (d) -NR⁹R¹⁰,
- (e) -NR⁹-COR¹⁰,
- 15 (f) -NR⁹-CO₂R¹⁰,
- (g) phenyl,
- (h) -CF₃,
- (i) -CHF₂,
- (j) -CH₂F, and
- 20 (k) -O-R⁹,
- (14) phenyl or heterocycle, wherein the phenyl or heterocycle is unsubstituted or substituted, wherein the substituents are independently selected from:
 - (a) -CO₂(C₁-6 alkyl),
 - 25 (b) hydroxy,
 - (c) halogen,
 - (d) -NR⁹R¹⁰,
 - (e) -NR⁹-COR¹⁰,
 - (f) -NR⁹-CO₂R¹⁰,
 - 30 (g) phenyl,
 - (h) -CF₃,
 - (i) -CHF₂,
 - (j) -CH₂F, and
 - (k) -O-R⁹,

Y and Z are independently selected from: C₁ alkyl, -O-, -S(O)_n- and -N(R⁹)-;

5 m is an integer selected from 1 and 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

4. The compound of Claim 1 wherein:

10 R¹ is selected from the group consisting of:

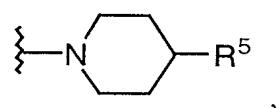
- (1) -CH₂-phenyl,
- (2) -CO-phenyl,
- (3) -CH₂-(2,4-dichlorophenyl),
- (4) -CO-(2,4-dichlorophenyl),
- 15 (5) -CH₂-(2-naphthyl),
- (6) -CO-(1-naphthyl),
- (7) -CH₂-indolyl, and
- (8) -CO-indolyl.

20 5. The compound of Claim 1 wherein:

R¹ is selected from the group consisting of:

- (1) -CH₂-phenyl,
- (2) -CO-phenyl,
- (3) -CH₂-(2,4-dichlorophenyl),
- 25 (4) -CH₂-(7-indolyl), and
- (5) -CO-(7-indolyl).

6. The compound of Claim 1 wherein:
R² is:

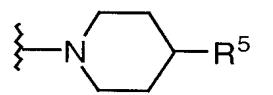


wherein R⁵ is selected from:

- (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- (2) -C₁-6alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with: halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl; and wherein the -C₁-6alkyl is optionally substituted with oxo, hydroxy, C₁-6alkoxy, acetoxy, or halogen,
- (3) -O-C₁-6alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- 10 (4) -C₁-4alkyl-O-C₁-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl, and
- (5) -C₁-4alkyl-S(O)_n-C₁-4alkyl-phenyl, wherein n is an integer selected from 0, 1 and 2, and wherein the phenyl is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl.

15 7. The compound of Claim 1 wherein:

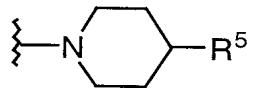
R² is:



20 wherein R⁵ is a selected from:

- (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- (2) -C₂-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro, trifluoromethyl, methyl or ethyl and wherein the -C₂-4alkyl is optionally substituted with oxo, hydroxy, halogen, or methoxy,
- (3) -C₁-3alkyl-O-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro, trifluoromethyl, methyl or ethyl, and
- (4) -C₁-3alkyl-S(O)_n-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro, trifluoromethyl, methyl or ethyl.

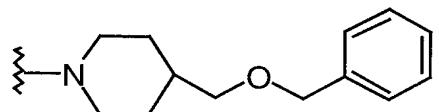
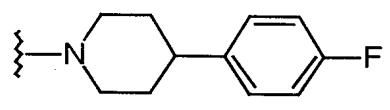
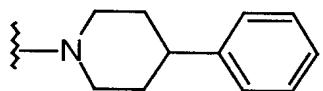
8. The compound of Claim 1 wherein:
 R² is:

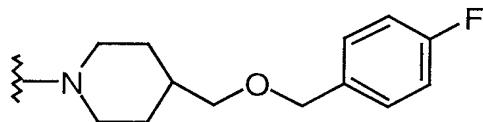


wherein R⁵ is selected from:

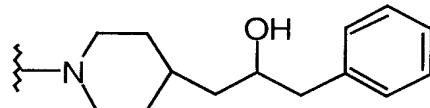
- 5 (1) phenyl, which is unsubstituted or substituted with halogen, hydroxy, C₁-6alkyl, C₁-6alkoxy, or trifluoromethyl,
- (2) -C₃-4alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro or methyl, and wherein the -C₃-4alkyl is optionally substituted with oxo, hydroxy, or methoxy,
- 10 (3) -C₁-3alkyl-O-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro or methyl, and
- (4) -C₁-3alkyl-S(O)_n-C₁-3alkyl-phenyl, wherein the phenyl is unsubstituted or substituted with chloro, fluoro or methyl.

15 9. The compound of Claim 1 wherein:
 R² is:





or



5

10. The compound of Claim 1 wherein:

R^3 is selected from the group consisting of:

- (1) $-CHO$,
- (2) $-CO-R^{16}$, wherein R^{16} is C₁₋₆ alkyl, wherein the alkyl is unsubstituted or substituted, wherein the substituents are independently selected from:
 - (a) $-CO_2(C_{1-6} \text{ alkyl})$,
 - (b) hydroxy,
 - (c) $-O-C_{1-6} \text{ alkyl}$,
 - (d) halogen, and
 - (e) phenyl,
- (3) $-CO_2-R^{16}$,
- (4) $-CONH_2$,
- (5) $-CONR^{16}R^{17}$, wherein R^{17} is hydrogen or is independently selected from the definitions of R^{16} ;
- (6) $-CONH-CO-R^{16}$,
- (7) $-C(R^{17})(OR^{16})(OR^{16})$,
- (8) $-C(R^{17})(SR^{16})(SR^{16})$,
- (9) $-C(R^{17})(OR^{14})(OR^{15})$, wherein R^{14} and R^{15} are joined together in a C₂₋₃ alkyl group to form a 5- or 6-membered ring which is substituted with R^{12} and R^{13} wherein:

R^{12} and R^{13} are independently selected from:

 - (a) hydrogen,

- (b) $-\text{CO}_2\text{R}16$,
- (c) hydroxy,
- (d) halogen,
- (e) $-\text{CF}_3$,
- 5 (f) $-\text{CHF}_2$,
- (g) $-\text{CH}_2\text{F}$,
- (h) C₁₋₆ alkyl, wherein the alkyl is unsubstituted or substituted, wherein the substituents are independently selected from:
 - (i) $-\text{CO}_2(\text{C}_{1-6} \text{ alkyl})$,
 - (ii) hydroxy,
 - (iii) $-\text{O-C}_{1-6} \text{ alkyl}$,
 - (iv) halogen, and
 - (v) phenyl,
- 10 (i) phenyl, unsubstituted or substituted, wherein the substituents are independently selected from:
 - (i) C₁₋₆ alkyl,
 - (ii) $-\text{CO}_2(\text{C}_{1-6} \text{ alkyl})$,
 - (iii) hydroxy,
 - (iv) $-\text{O-C}_{1-6} \text{ alkyl}$, and
 - (v) halogen,
- 15 (10) $-\text{C}(\text{R}17)(\text{SR}14)(\text{SR}15)$,
- (11) -cyclopentyl, which is substituted with R₁₂ and R₁₃,
- (12) -cyclohexyl, which is substituted with R₁₂ and R₁₃,
- (13) -tetrahydrofuryl, which is substituted with R₁₂ and R₁₃,
- 20 (14) -tetrahydropyranyl, which is substituted with R₁₂ and R₁₃.

11. The compound of Claim 1 wherein:

R³ is selected from:

- (1) $-\text{CH}(\text{OR}14)(\text{OR}15)$, wherein R₁₄ and R₁₅ are joined together in a C₂₋₃ alkyl group to form a 5- or 6-membered ring which is substituted with R₁₂ and R₁₃ wherein:
 - R₁₂ and R₁₃ are independently selected from:
 - (a) hydrogen,

(b) C₁-6 alkyl, wherein the alkyl is unsubstituted or substituted, wherein the substituents are independently selected from:

(i) -O-C₁-6 alkyl,
 (ii) halogen, and
 (iii) phenyl,

(c) phenyl, unsubstituted or substituted, wherein the substituents are independently selected from:

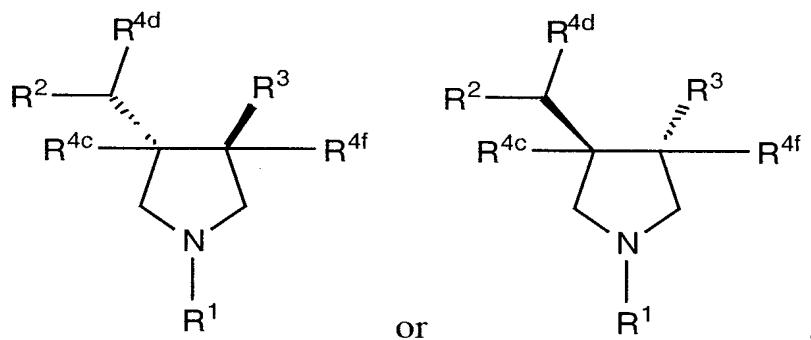
(i) C₁-6 alkyl,
 (ii) -O-C₁-6 alkyl,
 (iii) halogen, and

(2) -CH(SR¹⁴)(SR¹⁵),
 (3) -tetrahydrofuryl, which is substituted with R¹² and R¹³,
 (4) -tetrahydropyranyl, which is substituted with R¹² and R¹³.

12. The compound of Claim 1 wherein:

R^{4c}, and R^{4h} are each hydrogen and R^{4d} is selected from the group consisting of hydrogen, and -CH₃.

13. The compound of Claim 1 which is of the stereochemical configuration:



14. A compound which is selected from the group consisting of:

25 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-carboxypyrrolidine;

1-Benzyl-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(RS)-(ethoxy carbonyl)pyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-methoxycarbonylpyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-ethoxycarbonylpyrrolidine;

10 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-isopropoxycarbonylpyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-benzyloxycarbonylpyrrolidine;

15 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-formylpyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N-ethylaminocarbonyl)pyrrolidine;

20 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(N, N-diethylaminocarbonyl)pyrrolidine;

25 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-acetylpyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-benzoylpyrrolidine;

30 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(cyclopentyl)pyrrolidine;

1-(1-Methyl-7-indolecarbonoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinyl methyl)-4-(SR)-(cyclopentyl)pyrrolidine;

1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(cyclohexyl)pyrrolidine;

5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dithiolan-2-yl)pyrrolidine;

10 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-tetrahydrofuranyl)pyrrolidine;

15 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(2-tetrahydropyranyl)pyrrolidine;

20 1-(1-Methyl-7-indolecarbonyl)-3-(RS)-(4-(4-fluorophenyl)piperidinyl methyl)-4-(SR)-(1,3-dithiolan-2-yl)pyrrolidine;

25 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine;

30 1-(Benzyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylcarbonyl)-4-(SR)-(1,3-dioxolan-2-yl)pyrrolidine;

1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-methyl-1,3-dioxolan-2-yl)pyrrolidine;

1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-fluoromethyl-1,3-dioxolan-2-yl)pyrrolidine;

1-(2-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(4-methoxymethyl-1,3-dioxolan-2-yl)pyrrolidine;

5 1-(1-Naphthoyl)-3-(RS)-(4-(4-fluorophenyl)piperidinylmethyl)-4-(SR)-(1,3-dioxan-2-yl)pyrrolidine;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10 15. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

15 16. A method for modulation of chemokine receptor activity in a mammal comprising the administration of an effective amount of the compound of Claim 1.

17. A method for preventing infection by HIV, treating infection by HIV, delaying of the onset of AIDS, or treating AIDS comprising the administration to a patient of an effective amount of the compound of Claim 1.

20 18. A method for the prevention or treatment of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of the compound of Claim 1.

25 19. A method for the prevention or treatment of asthma, allergic rhinitis, dermatitis, conjunctivitis, atherosclerosis or rheumatoid arthritis which comprises the administration to a patient of an effective amount of the compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05341

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-structure

WEST/EAST-- subclass image

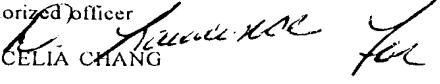
C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WO 99/09984 A1 (MERCK CO. INC.) 04 March 1999, see entire article.	1-19
A	EP 0 136 658 A2 (BOEHRINGER INGELHEM KG) 27 September 1984, see entire article.	1
A	JP 10-273489 A (SANKYO CO., LTD.) 01 October 1998, see entire document.	1-14
A	US 5,217,967 A (LEHR et al.) 08 June 1993, see entire article.	1-14
A	US 5,541,343 A (HIMMELSBACH et al.) 30 July 1996, see entire article.	1-14

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance		
E earlier document published on or after the international filing date	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed	*&*	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 APRIL 2000	13 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  CELIA CHANG
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05341

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

IPC7(7) A61K 31/47, 55,435, 445, 495; C07D 211/68, 217/02, 223/16, 401/06, 403/06

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/212, 213, 255, 278, 307, 321, 323, 326, 340; 546/17, 139, 194, 198, 208, 210, 256, 544/372, 540/594, 602

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/212, 213, 255, 278, 307, 321, 323, 326, 340; 546/17, 139, 194, 198, 208, 210, 256, 544/372, 540/594, 602